### Molecular in My Pocket...

#### Hematopathology

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### Myelodysplastic Syndromes (MDS)

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#### Mutation Details

- **Good Prognosis**:
  - SF3B1 mutation (strongly correlated with ring sideroblasts)
  - With SF3B1 mutation can diagnose MDS with ring sideroblasts (MDS-RA) with only 5% ring sideroblasts rather than 15% without the mutation

- **Intermediate Prognosis**:  
  - ASXL1, SRSF2, STAG2, EZH2, DNMT3A, TET2, TP53 mutation

- **Poor Prognosis**:  
  - ASXL1, SRSF2, STAG2, EZH2, DNMT3A, TET2, TP53 mutation

#### Progression Mutations

- RAS, FLT3, JAK2, NF1, RUNX1, ETV6, SETBP1

**Chronic Myelogenous Leukemia (CML)**

- t(9;22)(q34;q11.2) BCR-ABL1
  - Usually M-BCR (p210) breakpoint
  - Rarely m-BCR (p190) or m-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)

#### Polycythemia Vera (PV)

- JAK2 V617F (~50% 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 W515K/L (~5% of cases)

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Chronic Myelomonocytic Leukemia (CMML) (MDS/MPN “bridging” category)
- Most patients: TET2 (<50%), SRSF2 (~30-50%), ASXL1 (40-50%, poor prognosis if missense mutations are excluded), KRAS and NRAS (myeloproliferative phenotype), SETBP1 (poor prognosis), JAK2 (not specific)

Atypical Chronic Myeloid Leukemia (aCMML)
- Overlap MDS/MPN neoplasms
- BCR-ABL1 negative
- Cyto genetic: +8, i(17q), -7, del(7q), del(20q), +9, del(13q)
- Molecular genetics: SETBP1 (10-20%), exon 4 mutations with D868N most common, associated with -7 and i(17q), 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 PTPN11 (20-30%), KRAS and NRAS (75-80%) mutations
- Clinical NFI disease or NFI mutation
- Germ line CBL mutation (10-15%), Y371 common mutation hotspot

Myeloid/Lymphoid Neoplasms associated with Eosinophilia
- PDGFRα rearrangement (often del(4)(q12);IP11L-PDGFRα)
- FGFRL rearrangement (various partners)
- t(8;9)(p22;p24.1)PCMT1-JAK2

Myeloid Neoplasms with Germ line Predisposition
- AML with germ line CEBPA mutation
- Myeloid neoplasm with germ line DDX41 mutation
- Associated with platelet disorders
  - RUNX1, ANKRD26, ETVI6 mutation
  - Associated with other organ dysfunction
    - GATA2 mutation
    - JHML type mutations
- Langerhans histiocytosis, histiocytic sarcoma, disseminated juvenile xanthogranuloma, Erdheim-Chester disease, follicular dendritic cell sarcoma
- BAF160E mutation

T lymphoblastic leukemia/lymphoma (T-ALL)
- Translocations involving T-cell receptor (TCR); error during TCR gene rearrangements
  - t(9;34)(q34;q34) NUP214-ABL1 strictly associated with T-ALL (~60%)
  - MTC translocations (~6-8% cases)
  - NOTCH1 (70% cases), CDKN2A (cryptic deletions ~70% cases) mutations
  - Early T-precursor Acute Lymphoblastic Leukemia (ETP ALL)
  - FLT3, NRAS/KRAS, DNMT3A, IDH1/2
  - Anaplastic Large Cell Lymphoma, ALK-negative (ALCL, ALK-) (subset have rearrangement at 6q25 (region with DUSP22 and IRF4) - good prognosis
  - TP63 rearrangement - poor prognosis
  - Anaplastic Large Cell Lymphoma, ALK-positive (ALCL, ALK+)
    - Chromosome translocations involving ALK gene at 2p23
    - t(2;5)(p23;q35); ALK-NPM1
    - Other ALK rearrangements

B-cell Neoplasms

B Lymphoblastic Leukemia (B-ALL)
- Good prognosis
  - Hyperdiploid (extra chromosome copies are not random: X, 4, 14, 21 most common)
  - t(1;22)(p13;q22);ETVI6-RUNX1 (typically cryptic fusion)
  - Common in children, ~25% of B-ALL
- Intermediate prognosis:
  - t(5;14)(q31;q32); IL3-IGH, associated with eosinophilia
  - Poor Prognosis
    - t(9;22)(q34;q11.2); BCR-ABL1
      - Usually m-BCR (Most pediatric cases have p190; in adults, 50% is p190 and 50% is p210)
    - t(v;1q23); KMT2A rearranged
      - Most common leukemia in infants <1 year old; may occur in utero
    - Common translocation partners AF4 (4q21) and EFL (19p13)
  - frequent FLT3 overexpression
- Hypodiploid
  - Most commonly lost chromosomes include 3, 4, 7, 9, 13, 17, and 20
  - Worse prognosis: near haploid (25-29 chromosomes) and low hypodiploid (33-39 chromosomes)
- Intrachromosomal amplification of chromosome 21 (iAMP21)
  - 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

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 cyto genetic abnormalities (17p and 6q23 worse prognosis)
      - Complex karyotype correlates with poorer prognosis
      - BCL6 rearrangements more common in grade 3B tumors

B-cell Prolymphocytic Leukemia
- t(8;14)(q24;q32)
- Complex karyotypes
- MYC translocations (~50% cases)
  - Deletion 17p (~50% cases), associated with TP53 mutations, deletions of 13q14 (~30%), 11q23, rare trisomy 12.
  - Mutations in TP53 and ATM (~50%)

Mantle Cell Lymphoma (MCL)
- t(11;14)(q13;q32); CCND1-IGH
- Common secondary abnormalities: loss of 1p, 13q, 17p, gains in 3q.
  - Numerical abnormalities include +3, +12, -8, -9, -X, -Y
  - t(8;14)(q24;q32) occurs rarely and has worse prognosis; t(0;14) and CCND1 rearrangement is called a “double hit” MCL

Burkitt Lymphoma (BL)
- MYC rearrangements
  - t(8;14)(q24;q32); MYC-IGH
  - t(2;8)(p12;q24); IGK-MYC
  - t(8;22)(q24;q11); MYC-IGL

Hairy Cell Leukemia (HCL)
- BAF160E mutation (~95% of cases)
- >85% HCL cases demonstrate somatic hypermutation in VH genes
- MAP2K1 mutations = Hairy Cell Leukemia variant (HCL-v)

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
- Good Prognosis
  - del(13)(q14) most common cytogenetic abnormality
  - Mutated VH
  - Intermediate Prognosis
    - Trisomy 12 (a/w NOTCH1)
    - del(6q)
  - Poor Prognosis
    - 17p deletion
    - del(11)(q22-23) (a/w SF3B1)

Extranodal Marginal Zone Lymphoma, MALT type
- t(11;18)(q21;q11) – pulmonary and gastric MALT
  - t(14;18)(q32;q21) - orbital and salivary gland MALT
  - t(3;14)(p14;q32) - thyroid, orbital, skin MALT
  - t(1;14)(p12;q23)

Lymphoplasmacytic Lymphoma (LPL) and IgM Monoclonal Gammapathy of Unknown Significance (MUGS)
- 6q23 deletion most common cytogenetic finding in LPL
  - MYD88 p.L265P (~90% of cases)
  - CXCR4 mutation (~30% of LPL, ~20% of IgM MUGS)

Diffuse Large B-Cell Lymphoma (DLBCL)
- t(14;18)(q32;q27) is the most common translocation in DLBCL
- ALK-positive large B-cell lymphoma
  - t(2;17)(p23;q23); CLTC-ALK
- Double/Triple-Hit Lymphoma
  - MYC rearrangement with BCL2 and/or BCL6 rearrangement

T-cell Neoplasms

T-cell Large Granular Lymphocyte Leukemia (T-LGL)
- STAT3 mutation
- STAT5B mutation - poor prognosis

Peripheral T cell lymphoma, NOS (PTCL-NOS)
- TET2, DNMT3A, VAV1
- GATA3 vs TBI2 profiles
- Complex cytogenetic abnormalities common; t(5;9)(q33;q32) 7R+7Y in follicular variant
- Clonal rearrangements of TRB and TRG, IGH rearrangements in ~30% cases

Follicular T cell lymphomas (incl. angioimmunoblastic T cell lymphoma, ALTL)
- RHOD, GZMB, TET2, DNMT3A, IDH2
- T-cell Prolymphocytic leukemia (T-PLL; with inv(14) or t(4;14)ATM, STAT5B, JAK1, JAK3
- Complex karyotypes common with numerical and structural abnormalities including inv(14), t(6;14), t(8;10), -11, del(11q), -22, -13, TCL1, TCL1A (TCL1) rearrangements at 14q32. Multiple submicroscopic abnormalities