**ONCOLOGY: Acute Myeloid Leukemia**

**Work-up**

- Suspected acute leukemia

**Morphology**

- Flow cytometry

**Cytogenetics**

- Molecular genetic analysis

**Acute Myeloid Leukemia with Defining Genetic Abnormalities**

- **Acute promyelocytic leukemia with PML::RARA fusion**
  - Good prognosis
  - t(15;17)(q22;q11.2)
  - Blasts with granules +/− Auer rods (often multiple)
  - Other variants - Cells with regular nuclei, many granules, absence of Auer rods, pelgeroid neutrophils, strong MPO
    - NUMA1::RARA; t(11;17)(q13.4;q21.2)
    - NPM1::RARA; t(5;17)(q35.1;q21.2)
    - STAT5B::RARA; t(17;17)(q21.2;q21.2)
    - ZBTB16::RARA; t(11;17)(q23.2;q21.2)
  - Associated with disseminated intravascular coagulation
  - Sensitive to ATRA/arsenic trioxide
    - ZBTB16::RARA and STAT5B::RARA are ATRA resistant

- **AML with RUNX1::RUNX1T1 fusion; t(8;21)(q22;q22.1)**
  - Good prognosis
  - Blasts with basophilic cytoplasm, azurophilic granules and perinuclear hofs; may show pseudo-Chédiak-Higashi granules and/or single, long Auer rods with tapered ends
  - Neutrophils may show pseudo-Pelger-Huët nuclei and salmon pink granules
  - Presence of KIT mutation and CD56 expression associated with worse prognosis; ASXL1/2 mutations may also be seen

- **AML with CBFB::MYH11 fusion**
  - Good prognosis
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
  - Blasts with abnormal eosinophils (immature eosinophilic/basophilic granules, dense and purplish in color)
  - Secondary cytogenetic abnormalities include +22 and +8 (each occurring in 10-15% of cases), del(7q) and +21 (in 5%)
  - KIT mutations in exons 8 and 17 (in 30-40%); worse prognosis
  - Other mutations: NRAS (in 45%), KRAS (in 13%), FLT3 (in 14%)

- **AML with KMT2A rearrangement**
  - Intermediate prognosis
  - More than 80 KMT2A fusion partners described, with MLLT3, AFDN, ELL, and MLLT10 being most common
  - Adults often have high blast counts at presentation, usually with monocytic differentiation
  - In children, AML with KMT2A::MLLT3 and KMT2A::MLL10 show megakaryoblastic differentiation and/or low blast counts
  - May present with DIC, myeloid sarcoma, gingival hyperplasia
  - May need FISH/other molecular techniques for identification due to subtle translocations
  - MECOM overexpression is common; worse prognosis

- **AML with DEK::NUP214 fusion**
  - Poor prognosis
  - t(6;9)(p23;q34.1)
  - Blasts with/without monocyctic features
  - Associated with basophilia and multilineage dysplasia
  - FLT3-ITD mutations are common; may benefit from FLT3 inhibitors

- **AML with MECOM rearrangement**
  - Poor prognosis
  - inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)
  - May have normal or elevated platelet counts, hepatosplenomegaly
  - Peripheral blood may include hypogranular neutrophils with pseudo-Chédiak-Higashi granules and/or single, long Auer rods with tapered ends
  - May be associated with mutations of RAS/receptor tyrosine kinase signalling pathways (NRAS, PTPN11, FLT3, KRAS, NF1, KIT)
  - Other associated mutations: GATA2, RUNX1, SF3B1

- **AML with KMT2A::RUNX1 fusion**
  - Good prognosis
  - More than 80 KMT2A fusion partners described, with MLLT3, AFDN, ELL, and MLLT10 being most common
  - Adults often have high blast counts at presentation, usually with monocytic differentiation
  - In children, AML with KMT2A::MLLT3 and KMT2A::MLL10 show megakaryoblastic differentiation and/or low blast counts
  - May present with DIC, myeloid sarcoma, gingival hyperplasia
  - May need FISH/other molecular techniques for identification due to subtle translocations
  - MECOM overexpression is common; worse prognosis

- **AML with DEK::NUP214 fusion**
  - Poor prognosis
  - t(6;9)(p23;q34.1)
  - Blasts with/without monocyctic features
  - Associated with basophilia and multilineage dysplasia
  - FLT3-ITD mutations are common; may benefit from FLT3 inhibitors

- **AML with R8M15::MRTFA fusion**
  - Poor prognosis
  - t(1;12)(p13.3;q13.1)
  - Uncommon; may be congenital
  - Infants and children age <3 years
  - Small and large megakaryoblasts admixed with undifferentiated blasts; dense fibrosis

- **AML with BCR/ABL1 fusion**
  - 20% blasts required
  - De novo AML in patients with no evidence of CML before/after therapy
  - Present with less splenomegaly, less basophilia, lower cellularity, fewer dwarf megakaryocytes, normal M:E ratio compared with blast transformation of CML
  - Most cases show the p210 fusion (most commonly b2a2 and b3a2 fusions); minority show p190 fusion
  - Associated with -7, +8 and complex karyotypes
  - May be associated with NPM1 and KIT mutations
  - Present with less splenomegaly, less basophilia, lower cellularity, fewer dwarf megakaryocytes, normal M:E ratio compared with blast transformation of CML

**Mixed phenotype acute leukemia**

- Acute myeloid leukemia
- B or T lymphoblastic leukemia/lymphoma

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### Acute Myeloid Leukemia with Defining Genetic Abnormalities (cont’d)

**AML with NPM1 mutation**
- Overall prognosis good; poorer prognosis with presence of FLT3-ITD +/- DNMT3A
- Blasts often show monocytic features
- Multilineage dysplasia seen in up to 25% of cases
- Often associated with normal karyotype
- del(9q), +8 seen in 5-15% of cases
- Secondary mutations include FLT3, DNMT3A, IDH1/2, KRAS, NPM1

**AML with NUP98 rearrangement**
- Rearrangement may be cryptic

**AML with mutated TP53**
- Very poor prognosis
- Typically associated with complex karyotype
- Although multi-hit TP53 is required for MDS with mutated TP53, in AML and MDS/AML with mutated TP53, any pathogenic TP53 mutation VAF >10% is sufficient.
- Pure erythroid leukemia is typically associated with TP53 mutations, and these cases should be classified as AML with mutated TP53.

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### Myeloid/Lymphoid Neoplasms with eosinophilia and tyrosine kinase gene fusions

- Broad range of histologic types – MPN, MDS, MDS/MPN, AML, MPAL, B-ALL, T-ALL
- Eosinophilia common feature but may be absent in some cases
- Sensitive to tyrosine kinase inhibitor therapy
- Defining genetic abnormalities
  - **PDGFRα rearrangement** (often del(4)(q12q12); FIP1L1::PDGFRα)
  - **PDGFRα rearrangement** (often t(5;12)(q31.1;q12); EGFR::PDGFRα)
  - **FGFR1 rearrangement**
  - **JAK2 rearrangement** (often t(8;9)(p22;p24.1); PCM1::JAK2)
  - **FLT3 rearrangement**
  - **ETV6::ABL1 fusion**
  - Other defined TK fusions: **ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET**

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### Myeloid neoplasms post cytotoxic therapy

- Poor prognosis
- Requires a documented history of chemotherapy (e.g. alkylating agents, topoisomerase II inhibitors, antimetabolites, antituibulin agents) or large-field radiation therapy for an unrelated condition
- De novo AML with defining genetic abnormalities post cytotoxic therapy should be assigned to this category
- Majority associated with TP53 mutations; worse outcomes with biallelic (multi-hit) TP53 alterations
- Less frequent mutations involving genes such as PPM1D or DNA-damage response genes require consideration of a germline predisposition

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### Myeloid neoplasms associated with germline predisposition

- **Myeloid neoplasm predisposition without a pre-existing platelet disorder or organ dysfunction**
  - Germline **CEBPA** P/LP variant (CEBPA-associated familial AML)
  - Germline **DDX41** P/LP variant
  - Germline **TP53** P/LP variant (Li-Fraumeni syndrome)
- **Myeloid neoplasm predisposition and pre-existing platelet disorder**
  - Germline **RUNX1** P/LP variant (familial platelet disorder with associated myeloid malignancy)
  - Germline **ANKRD26** P/LP variant (Thrombocytopenia 2)
  - Germline **ETV6** P/LP variant (Thrombocytopenia 5)

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### Myeloid neoplasms with germline predisposition and potential organ dysfunction

- Germline **GATA2** P/LP variant (GATA2 deficiency)
- Bone marrow failure syndromes
  - Severe congenital neutropenia (SCN)
  - Shwachman-Diamond syndrome (SDS)
  - Fanconi anemia (FA)
- Telomere biology disorders
- RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome, or Noonan syndrome-like disorders)
- Down Syndrome
- Germline **SMAD9** P/LP variant (MIRAGE syndrome)
- Germline **SAMD9L** P/LP variant (SAMD9L-related ataxia pancytopenia syndrome)
- Germline **BLM** P/LP variant (Bloom syndrome)

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*Prepared by the Association for Molecular Pathology Training and Education Committee. For more educational resources, see: www.amp.org/AMPEducation*