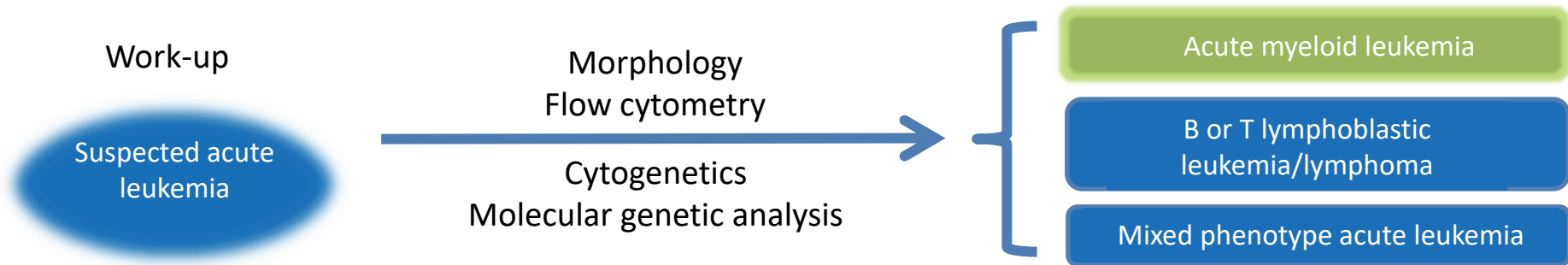


ONCOLOGY: Acute Myeloid Leukemia



Acute Myeloid Leukemia with Defining Genetic Abnormalities

Acute promyelocytic leukemia with *PML::RARA* fusion

- Good prognosis
- t(15;17)(q13.4;q21.2)
- Kidney-shaped or bilobed blasts with granules +/- Auer rods (often multiple)
- Other variants - Cells with regular nuclei, many granules, absence of Auer rods, pelgeroid neutrophils, strong MPO
 - *RF2BP2::RARA*; t(1;17)(q42.3;q21.2)
 - *NUMA1::RARA*; t(11;17)(q13.4;q21.2)
 - *NPM1::RARA*; t(5;17)(q35.1;q21.2)
 - *STAT5B::RARA* or *STAT3::RARA*; t(17;17)(q21.2;q21.2), inv(17), del(17)
 - *ZBTB16::RARA*; t(11;17)(q23.2;q21.2)
 - *TBL1XR1::RARA*; t(3;17)(q26.3;q21.2)
 - *FIP1L1::RARA*; t(4;17)(q12;q21.2)
 - *BCOR::RARA*; t(X;17)(p11.4;q21.2)
- Associated with disseminated intravascular coagulation
- Sensitive to ATRA/arsenic trioxide
 - some variant, such as *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
- ≥ 70% have additional karyotypic abnormality: -X, del(9q)
- Presence of *KIT* mutation and CD56 expression associated with worse prognosis; *ASXL1/2*, *KRAS*, *NRAS* mutations may also be seen

AML with *CBFB::MYH11* fusion

- Good prognosis
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
 - likely need FISH/RT-PCR – subtle rearrangement
- Blasts with abnormal eosinophils (immature eosinophilic/basophilic granules, dense and purple-violet 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% worse prognosis)

AML with *KMT2A* rearrangement

- ≥80 *KMT2A* fusion partners described, with *MLLT3*, *AFDN*, *ELL*, and *MLLT10* being most common; most poor prognosis
- *KMT2A::MLLT3*; t(9;11)(p21.3;q23.3); Intermediate prognosis
- Adults often have high blast counts at presentation, usually with monocytic differentiation
- In children, AML with *KMT2A::MLLT3* and *KMT2A::MLLT10* 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); mostly sole karyotypic abnormality
- Blasts with/without monocytic 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-Pelger-Huët nuclei, giant and hypogranular platelets with bare megakaryocytic nuclei
- Associated with increased dysplastic megakaryocytes with monolobated or bilobed nuclei, and multilineage dysplasia
- Often associated with -7 (>50% of cases), del(5q) and complex karyotypes
- Also associated with mutations of RAS/receptor tyrosine kinase signaling pathways (*NRAS*, *PTPN11*, *FLT3*, *KRAS*, *NF1*, *CBL*, *KIT*)
- Other associated mutations: *GATA2*, *RUNX1*, *SF3B1*

AML with *RBM15::MRTFA* fusion

- Poor prognosis
- t(1;22)(p13.3;q13.1); mostly sole karyotypic abnormality
- 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 *FLT3*-ITD, loss of *IKZF1* and *CDKN2A* and cryptic deletions in *IGH* and *TRG* genes (not seen in blast transformation of CML)

Acute Myeloid Leukemia with Defining Genetic Abnormalities (cont'd)	Acute myeloid leukemia, myelodysplasia-related (AML-MR)	
<p>AML with <i>NUP98</i> rearrangement</p> <ul style="list-style-type: none"> >30 fusion partners Rearrangement may be cryptic Many associated with overexpression of <i>HOXA9</i>; poor prognosis <p>AML with <i>NPM1</i> mutation</p> <ul style="list-style-type: none"> Overall good prognosis; poorer prognosis with presence of <i>FLT3</i>-ITD +/- <i>DNMT3A</i> Blasts often show monocytic features Multilineage dysplasia seen in up to 25% of cases Usually associated with normal karyotype del(9q), +8 seen in 5-15% of cases Secondary mutations include <i>FLT3</i>, <i>DNMT3A</i>, <i>IDH1/2</i>, <i>KRAS</i>, <i>NRAS</i> Up-regulation of <i>HOX</i> gene <p>AML with mutated <i>TP53</i></p> <ul style="list-style-type: none"> Very poor prognosis Typically associated with complex karyotype Although multi-hit <i>TP53</i> is required for MDS with mutated <i>TP53</i>, in AML and MDS/AML with mutated <i>TP53</i>, any pathogenic <i>TP53</i> mutation VAF >10% is sufficient. 	<ul style="list-style-type: none"> Pure erythroid leukemia is typically associated with <i>TP53</i> mutations, and these cases should be classified as AML with mutated <i>TP53</i>. <p>AML with <i>CEBPA</i> mutation</p> <ul style="list-style-type: none"> 20% blasts required Favorable prognosis Includes biallelic (bi<i>CEBPA</i>) and single mutations located in the basic leucine zipper region of the gene (smbZIP-<i>CEBPA</i>) No distinct morphologic features (usually have features of AML with/without maturation) Higher expression of HLA-DR, CD7 and CD15 Presence of bi<i>CEBPA</i> should raise possibility of germline mutation >70% of cases associated with normal karyotype; del(9q) may also be seen <i>GATA2</i> mutations seen in 39% of cases, <i>FLT3</i>-ITD in 5-9% of cases 	<p>AML with other defined genetic alterations</p> <ul style="list-style-type: none"> "Landing spot" for emerging or rare entities <p>Diagnosis requires:</p> <ul style="list-style-type: none"> ≥20% blasts required by WHO; 10% blasts by ICC Either: history of MDS or MDS/MPN, or MDS-related cytogenetic abnormality or somatic mutation Absence of prior cytotoxic or radiation therapy for unrelated disease or AML-defining recurrent genetic abnormality <p>4 subclassifications (ICC only)</p> <ul style="list-style-type: none"> AML with myelodysplasia-related cytogenetic abnormalities AML and MDS/AML with myelodysplasia-related gene mutations AML and MDS/AML with mutated <i>TP53</i> AML, NOS <p>ML-MR-defining cytogenetic abnormalities</p> <ul style="list-style-type: none"> Complex karyotype (≥3 abnormalities) del(5q), t(5q) -7, del(7q) del(11q) del(12p) -13 or del(13q) Isochromosome 17q, del(17p) idic(X)(q13) <p>AML-MR-defining somatic mutations</p> <ul style="list-style-type: none"> <i>ASXL1</i> <i>BCOR</i> <i>EZH2</i> <i>SF3B1</i> <i>SRSF2</i> <i>STAG2</i> <i>U2AF1</i> <i>ZRSR2</i> <i>RUNX1</i> (ICC only)
Eosinophilia	Secondary myeloid neoplasms	
<p>Myeloid/Lymphoid Neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)</p> <ul style="list-style-type: none"> 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 (TKI) therapy Defining genetic abnormalities <ul style="list-style-type: none"> <i>PDGFRA</i> rearrangement (often del(4)(q12q12); <i>FIP1L1::PDGFRA</i>) <i>PDGFRB</i> rearrangement (often t(5;12)(q32;p12); <i>ETV6::PDGFRB</i>) <i>FGFR1</i> rearrangement <i>JAK2</i> rearrangement (often t(8;9)(p22;p24.1); <i>PCM1::JAK2</i>) <i>FLT3</i> rearrangement <i>ETV6::ABL1</i> fusion (separate from B-ALL with <i>ETV6::ABL1</i>) and other <i>ETV6</i> rearrangement (<i>ETV6::FGFR2</i>; <i>ETV6::LYN</i>; <i>ETV6::NTRK3</i>; <i>RANBP2::ALK</i>) Other MLN-TK (more is accrued): <i>BCR::RET</i>; <i>FGFR1OP::RET</i> Mostly, long-term survival option is bone marrow transplant 	<p>Myeloid neoplasms post cytotoxic therapy (MN-pCT)</p> <ul style="list-style-type: none"> Poor prognosis Requires a documented history of chemotherapy (e.g. alkylating agents, topoisomerase II inhibitors, antimetabolites, antitubulin agents) or large-field radiation therapy for an unrelated condition <i>De novo</i> AML with defining genetic abnormality, such as <i>NNPM1</i> mutation and CBF AML, post cytotoxic therapy should be assigned to this category based on medical history Majority AML-pCT and MDS-pCT associated with <i>TP53</i> mutations; worse outcomes with biallelic (multi-hit) <i>TP53</i> alterations Less frequent mutations involving genes such as <i>PPM1D</i> or DNA-damage response genes require consideration of a germline predisposition 	<p>Myeloid neoplasms associated with germline predisposition</p> <ul style="list-style-type: none"> Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction <ul style="list-style-type: none"> Germline <i>CEBPA</i> P/LP variant (CEBPA-associated familial AML) Germline <i>DDX41</i> P/LP variant Germline <i>TP53</i> P/LP variant (Li-Fraumeni syndrome) Myeloid neoplasms with germline predisposition and pre-existing platelet disorder <ul style="list-style-type: none"> Germline <i>RUNX1</i> P/LP variant (familial platelet disorder with associated myeloid malignancy, FPD-MM) Germline <i>ANKRD26</i> P/LP variant (Thrombocytopenia 2) Germline <i>ETV6</i> P/LP variant (Thrombocytopenia 5) <p>Myeloid neoplasms with germline predisposition and potential organ dysfunction</p> <ul style="list-style-type: none"> Germline <i>GATA2</i> P/LP variant (<i>GATA2</i>-deficiency) Bone marrow failure syndromes <ul style="list-style-type: none"> 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 <i>SMAD9</i> P/LP variant (MIRAGE syndrome) Germline <i>SAMD9L</i> P/LP variant (<i>SAMD9L</i>-related ataxia pancytopenia syndrome) biallelic germline <i>BLM</i> P/LP variant (Bloom syndrome)