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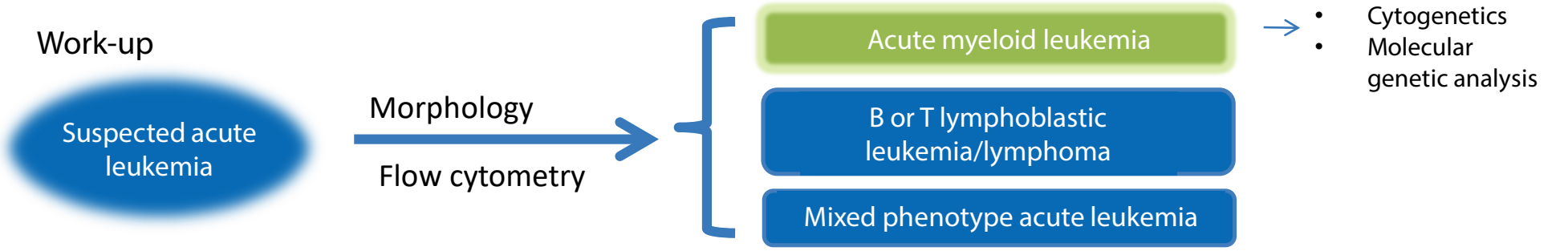
ONCOLOGY: *Acute Myeloid Leukemia*



Acute Myeloid Leukemia with Recurrent Genetic Abnormalities

Good prognosis

**Acute promyelocytic leukemia
- Associated with disseminated intravascular coagulation (DIC)
- Bilobed blasts with granules +/- Auer rods (often multiple)
- Sensitive to ATRA/arsenic trioxide
- *PML/RARA*; t(15;17)(q24.1;q21.2)
- Other variants:
  - *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* (formerly *PLZF/RARA);* t(11;17)(q23.2;q21.2)
  - Cells with regular nuclei, many granules, absence of Auer rods, pelgeroid neutrophils, strong MPO
  - *ZBTB16/RARA* and *STAT5B/RARA* are ATRA resistant

Core Binding Factor (CBF) AML
- *RUNX1/RUNX1T1*; t(8;21)(q22;q22.1)
- Blasts with basophilic cytoplasm, azurophilic granules and perinuclear hofs; may show pseudo-Chédiak-Higashi granules
- Neutrophils may show pseudo-Pelger-Huët nuclei and salmon pink granules
- Often single, long Auer rods with tapered ends
- Presence of *KIT* mutation and CD56 expression associated with worse prognosis
- *ASXL1/2* mutations may also be seen
- *CBFB/MYH11*; inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
- Blasts with abnormal eosinophils (showing immature eosinophilic/basophilic granules, dense and purple-violet in color)
- May be a subtle rearrangement only seen with FISH or RT-PCR
- Secondary cytogenetic abnormalities include +22 and +8 (each occurring in 10-15% of cases), del(7q) and +21 (in 5% of cases)
- *KIT* mutations in exons 8 and 17 found in 30-40% of cases; worse prognosis
- Other mutations: *NRAS* (45% of cases), *KRAS* (13% of cases), *FLT3* (14% of cases)

Intermediate prognosis

AML with t(9;11)(p21.3;q23.3); *KMT2A/MLLT3*
- Often monoblasts and promonocytes
- May present with DIC, myeloid sarcoma, gingival hyperplasia
- >120 different translocations involving *KMT2A*
- Translocations involving *MLLT1*, *MLLT10*, *AFDN* or *ELL* often result in AML, although translocations involving *KMT2A* may also result in lymphoblastic leukemia
- Translocations may be subtle, requiring FISH/other molecular techniques for identification
- *MECOM* overexpression is common; worse prognosis

Poor prognosis

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

AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
- 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 monosomy 7 (>50% of cases), del(5q) and complex karyotypes
- Also associated with mutations of RAS/receptor tyrosine kinase signalling pathways (*NRAS, PTPN11, FLT3, KRAS, NF1, KIT*)
- Other associated mutations: *GATA2, RUNX1, SF3B1*

AML with recurrent genetic abnormalities (cont'd)

AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); *RBM15/MKL1*

- Uncommon entity; may be congenital
- Restricted to infants and children aged ≤3 years)
- Small and large megakaryoblasts admixed with undifferentiated blasts
- Presence of dense fibrosis requiring correlation with core biopsy
- Poor prognosis

AML with *BCR/ABL1*

- Provisional entity
- *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 gene mutations

AML with mutated *NPM1*

- 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*, *NRAS*
- Overall good prognosis; poorer prognosis with presence of *FLT3*-ITD +/- *DNMT3A*

AML with biallelic mutation of *CEBPA*

- No distinct morphologic features (usually have features of AML with/without maturation)
- Higher expression of HLA-DR, CD7 and CD15
- Presence of biallelic *CEBPA* should raise possibility of germline mutation
- >70% of cases associated with normal karyotype; del(9q) may also be seen
- *GATA2* mutations seen in 39% of cases, *FLT3*-ITD in 5-9% of cases
- Biallelic mutation associated with good prognosis

AML with mutated *RUNX1*

- May be AML with minimal differentiation, AML with maturation or show monocytic features
- Mutations may occur with +8 and +13
- Other associated mutations : *ASXL1*, *KMT2A* partial tandem duplication, *FLT3*-ITD, *IDH1* R132, *IDH2* R140 and R172, *SRSF2*, *EZH2* and *STAG2*
- Subset of these patients have germline *RUNX1* mutations; assess family history
- Show poor prognosis

AML with myelodysplasia-related changes

Diagnosis requires:

- ≥20% blasts (blood/bone marrow)
- Either: History of MDS or MDS/MPN OR MDS-related cytogenetic abnormality OR multilineage dysplasia (>50% dysplasia in ≥2 lineages)
- Absence of prior cytotoxic or radiation therapy for unrelated disease OR AML-defining recurrent cytogenetic abnormality
- May be associated with mutations of *U2AF1*, *ASXL1*, *TP53* (latter two mutations worsen prognosis)

MDS-defining cytogenetic abnormalities

- Complex karyotype (≥3 abnormalities)
- Unbalanced abnormalities
  - -7 or del(7q)
  - del(5q) or t(5q)
  - Isochromosome 17q or t(17q)
  - -13 or del(13q)
  - del(11q)
  - del(12p) or t(12p)
  - idic(X)(q13)
- Balanced abnormalities
  - t(11;16)(q23.3;p13.3)
  - t(3;21)(q26.2;q22.1)
  - t(1;3)(p36.3;q21.2)
  - t(2;11)(p21;q23.3)
  - t(5;12)(q32;p13.2)
  - t(5;7)(q32;q11.2)
  - t(5;17)(q32;p13.2)
  - t(5;10)(q32;q21)
  - t(3;5)(q25.3;q35.1)

Therapy-related myeloid neoplasms

- Occurs as a complication of cytotoxic (e.g. alkylating agents, topoisomerase II inhibitors) and/or radiotherapy for neoplastic/non-neoplastic disorders
- May also be associated with antimetabolites (thiopurines, mycophenolate mofetil, fludarabine) and antitubulin agents (vincristine, vinblastine, vindesine, paclitaxel, docetaxel), hydroxyurea, L-asparagine, and purine analogues)
- Associated with abnormal karyotype, most often del(5q), -7, del(7q) in >70% of cases
- >80% of cases with del(5q) have *TP53* mutations or losses with del(17p) or -17
- 20-30% of cases have balanced translocations including t(15;17) and inv(16)
- Mutated genes of unknown significance include *TET2*, *PTPN11*, *IDH1/2*, *NRAS*, and *FLT3*
- Poor prognosis

Other

Myeloid/Lymphoid Neoplasms associated with Eosinophilia

- *PDGFRA* rearrangement (often del(4)(q12q12); *FIP1L1/PDGFRA*)
- *PDGFRB* rearrangement (often t(5;12)(q31~33;p12) ;*ETV6/PDGFRB*)
- *FGFR1* rearrangement (various partners)
- t(8;9)(p22;p24.1);*PCM1/JAK2*

Myeloid Neoplasms with Germline Predisposition

- AML with germline *CEBPA* mutation
- Myeloid neoplasm with germline *DDX41* mutation
- Associated with platelet disorders
  - *RUNX1*, *ANKRD26*, *ETV6* mutations
- Associated with other organ dysfunction
  - *GATA2* mutation
  - JMML type mutations

Prepared by the Association for Molecular Pathology Training and Education Committee
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