WHO Classification of Myeloid Neoplasms with Defined Molecular Abnormalities

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- Incorporates new information that has emerged since publication of 3rd edition--2001
  - Major changes / revisions in 4th edition
    - Addition of new entities --mostly defined by genetics
    - New defining criteria for some diseases
  - Minor changes / revisions in 4th edition
    - New nomenclature for some “old diseases”
    - Refinements in definitions
      - Monoblast vs. promonocyte vs. monocyte
      - Ring sideroblast
Molecular Analysis of Myeloid Neoplasms

- Detection and identification of translocations
  - BCR-ABL, FLT1L1-PDGFRα, PML-RARα, etc.

- Detection and identification of gene mutations
  - JAK2, KIT, FLT3, NPM1, CEBPA, etc.

- Detection of minimal residual disease
  - Fusion genes and gene mutations

- Gene expression profiling
Groups of Myeloid Neoplasms in the WHO Classification

- Acute Myeloid Leukemia (AML) and Related Precursor Neoplasms
- Myelodysplastic Syndromes
- Myelodysplastic / Myeloproliferative Neoplasms
- Myeloproliferative Neoplasms
- Myeloid and Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRA, PDGFRB or FGFR1
Acute Myeloid Leukemia
Acute Myeloid Leukemia and Related Precursor Neoplasms

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML not otherwise specified (NOS)
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
AML With Recurrent Genetic Abnormalities--WHO 4th Edition

- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16); CBFB-MYH11
- Acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARα
- AML with t(9;11)(p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3); RPN1-EVI1
- AML with t(1;22)(p13;q13); RBM15-MKL1
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA
AML With Recurrent Genetic Abnormalities

- Predominantly in younger individuals
- Favorable clinical behavior and response to therapy

- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22); CBFB-MYH11 or t(16;16)(p13.1;q22)
- Acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARα
- AML with t(9;11)(p22;q23); MLLT3-MLL*

* t(9;11) has intermediate prognosis
AML with t(8;21); RUNX1-RUNX1T1

- ~5% of AML (40% of karyotypically abn. AML with maturation)
- Characteristic morphologic features
- Frequent CD19(+) and PAX5(+); CD56(+) and TdT(+) in some cases
- Favorable prognosis
AML with inv(16)(p13;q22) - MYH11-CBFβ

- 5% to 8% of AML
- Myelomonocytic morphologic features
- Increased marrow and dysplastic eosinophils
- Frequent CD2 expression
- Favorable prognosis
Figure 1. Banding Patterns and Partial Karyotype of Chromosome 16.

Panel A shows the mechanism of inversion and banding pattern of the inverted chromosome 16.

Panel B shows a partial karyotype of Giemsa-stained and quinacrine-banded metaphase cells showing the normal and inverted chromosome 16 (left, Patient 168; right, Patient R-1).
Promyelocytic Leukemia with t(15;17); PML-RARα

- 5% to 8% of AML
- Leukemic cells are abnormal promyelocytes
  - Hypergranular
  - Microgranular
- Reniform nuclei
- Single cells with multiple Auer rods
- CD34(-) and HLADR(-), CD2(+) and CD56(+) in some cases
- Favorable prognosis--Responds to ATRA
AML with t(9;11) ; MLLT3-MLL

- 9% to 12% of AML in children; 2% in adults
- May present with DIC; extramedullary disease
- Usually monocytic features
- Fusion gene involving MLL with MLLT3
- Intermediate prognosis
80 different translocations involving *MLL* in acute leukemia

> 50 different partner genes

*MLLT3* most common partner in AML t(9;11)

~ 1/3 of *MLL* translocations are cryptic

Specific variant abnormality should be specified, e.g., t(11;19)(q23;p13.3); *MLL-ENL*

Therapy related AML with *MLL* abnormality
AML With Recurrent Genetic Abnormalities-- “New Categories”

- AML with \( t(6;9)(p23;q34); \) DEK-NUP214

- AML with \( \text{inv}(3)(q21q26.2); \) RPN1-EVI1 or \( t(3;3)(q21;q26.2) \)

- AML (megakaryoblastic) with \( t(1;22)(p13;q13); \) RBM15-MKL1
AML with t(6;9)(p23;q34); DEK-NUP214

- AML with maturation or myelomonocytic (90%)
- High WBC (m - 48 X 10⁹/L)
- Association with basophil component and TdT+
- Young age for AML (m - 24 yrs.)
- Poor prognosis (50% CR, median survival 16 months)
AML with inv(3)(q21q26.2) or t(3;3); RPN1-EVI1

- De novo AML or evolves from an MDS
- Normal or elevated platelet count
- Increased and atypical megakaryocytes
  - Mono- or bi-lobated nuclei
- multilineage dysplasia
- Aggressive disease with short survival
AML (Megakaryoblastic) with t(1;22); RBM15-MKL1

- Less than 1% of AMLs; usually occurs in infants
- Marked organomegaly
- Prominent myelofibrosis
- May show a stromal pattern of BM infiltration resembling a metastatic tumor
- ? Prognosis; recent reports favorable
Cytogenetics of AML

- ~60% of cases of AML have conventional (karyotype) cytogenetic abnormalities
- ~30% have recurrent abnormalities
- ~40% have a normal karyotype
- Many of those with a normal karyotype have either cryptic translocations / inversions / deletions or specific gene mutations
Gene Mutations and Expression Changes in Cytogenetically Normal AML

**Genetic Alteration**
- NPM1 mutation
- CEBPA mutation
- FLT3-ITD
- MLL-PTD
- BAALC over-expression
- ERG over-expression

**Prognostic Significance**
- Favorable
- Favorable
- Unfavorable
- Unfavorable
- Unfavorable
Activating Mutations of FLT3 in AML

- Most common somatic mutations observed in AML

- Mutations result from:
  - An internal tandem duplication (ITD) of the juxta-membrane domain (FLT3/ITD) (20% to >35%-adults)
  - Point mutation of the activation loop domain (FLT3/ALM) (~7%)

- Unfavorable prognosis for patients with FLT3/ITD
  - Significantly shorter DFS, and OS than patients that do not harbor FLT3/ITD
  - Very poor prognosis when coupled with no expression of FLT3 wild-type
  - FLT3-targeted agents are emerging as possible therapeutic options
NPM1 Mutations in AML

- Encodes for a multifunctional nucleocytoplasmic shuttling protein that is localized mainly in the nucleolus
- NPM1 over-expressed in the cytoplasm in AML
- NPM1 gene mutations are found in 50% to 60% of AML with normal cytogenetics
- 40% of patients harboring NPM1 mutations also carry FLT3/ITD
Features of AML with NPM1 Mutations

- Predominance of females
- High blood leukocyte counts
- CD34(-)
- Patients with NPM1 mutations without FLT3/ITD have better CR rates, EFS, and OS than patients without NPM1 mutations
- The prognostic effect of NPM1 mutations is diminished in patients with a FLT3/ITD
Acute Myeloid Leukemia with Mutated CEBPA

- 6% to 15% of AMLs (15% to 18% of AMLs with a normal karyotype)
- Usually AML with or without maturation
- CD7 expression in ~50% to 70% of cases
- FLT3-ITD mutations in 20% to 30%
- Favorable prognosis
Other Changes in the Classification of AML and Related Neoplasms

- Addition of: Myeloid Proliferations Related to Down Syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukemia/MDS associated with Down syndrome
Transient Abnormal Myelopoiesis (TAM) In Down Syndrome

- TAM occurs in neonates
  - Indistinguishable from AML
  - Megakaryoblastic component
  - Spontaneous remission in 2-14 wks.
  
- Clonal disorder—GATA1 mutations

- Evolution to AML in some cases
Myeloproliferative Neoplasms
WHO Classification of Myeloproliferative Neoplasms

- Chronic myelogenous leukemia, BCR-ABL1
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia, NOS
- Mastocytosis
- Myeloproliferative neoplasm, unclassifiable
Major Changes in the Classification of Myeloproliferative Neoplasms

- Myeloproliferative Disease has been changed to “Myeloproliferative Neoplasm”
- Mastocytosis has been included as a MPN
- Criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis are changed to include:
  - JAK2 and similar activating (gain of function) mutations
  - Pertinent histologic features of the BM biopsy
  - Platelet count threshold for ET is lowered to 450x10^9/L
MPN and Other Myeloid Neoplasms Associated with Mutation/Rearrangement of Tyrosine Kinase Genes

- Chronic myelogenous leukemia -- ABL1
- Polycythemia vera -- JAK2 V617F, JAK exon12
- Primary myelofibrosis -- JAK2 V617F, MPL W151L/K
- Essential thrombocythemia -- JAK2 V617F, MPL W151L/K
- Mastocytosis -- KIT D816V
- Myeloid neoplasms with eosinophilia -- PDGFRA, PDGFRB, FGFR1
Myeloid and Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRA, PDGFRB, or FGFR1

- A new disease group in the revised WHO classification that includes 3 entities
  - Myeloid and lymphoid neoplasms with PDGFRA rearrangement
  - Myeloid neoplasms with PDGFRB rearrangement
  - Myeloid and lymphoid neoplasms with FGFR1 abnormalities
Myeloid Neoplasm with FIP1L1-PDGFRA (Chronic Eosinophilic Leukemia)
Myeloid and Lymphoid Neoplasms with PDGFRA Rearrangement

- Most common is FIP1L1-PDGFRα resulting from a cryptic del(4)(q12)
- Detected by RT-PCR or FISH for CHIC2
- Rarely other partner genes-KIF5B, STRN, etc
- Rare disease; M:F ratio is ~ 17:1
- May present as CEL, CEL with mastocytosis, AML or T-ALL
- Symptoms/damage related to hypereosinophilia
- Highly responsive to tyrosine kinase inhibitors
Myeloid Neoplasms with PDGFRB Rearrangement

- Usually a t(5;12)(q31-33;p12) with formation of an ETV6-PDGFRB fusion gene
- Numerous other partner genes--all rare
- CMML with eosinophilia most common
- Occasionally other MPN
- Responsive to tyrosine kinase inhibitors
Myeloid and Lymphoid Neoplasms with FGFR1 Abnormalities

- Most commonly a t(8;13)(p11;q12) resulting in a ZNF198-FGFR1 fusion gene
- Other partner genes less common
- May have CEL, AML, T- or B-LBL/leukemia
- 90% have eosinophilia
- Not responsive to tyrosine kinase inhibitors
- Prognosis is poor
Diagnosis of Myeloid Neoplasms-2009

- Multidisciplinary approach to diagnosis
  - Morphology
  - Immunophenotyping
  - Cytogenetics / molecular cytogenetics
  - Molecular testing
- Revised WHO classification--2008
- More genetic / molecular categories and prognostic indicators
- Improved therapies and survivals
  - More genetic and immunotherapy targets
  - Improved chemotherapy protocols
THE END

THANK YOU
Major Changes in AML with Recurrent Genetic Abnormalities

- New categories:
  - AML with $t(6;9)(p23;q34); DEK-NUP214$
  - AML with $\text{inv}(3)(q21q26.2)$ or $t(3;3); RPN1-EV11$
  - AML with $t(1;22)(p13;q13); RBM15-MKL1$

- Provisional categories:* 
  - AML with mutated NPM1
  - AML with mutated CEBPA

*Examination for FLT3 ITD is recommended in all cytogenetically normal AML
Figure 7. Differential expression of select genes among VxInsight clusters

Topoisomerase II Inhibitor-Related AML

- Median 2.5 to 3 years after treatment
- Rarely MDS
- Usually monocytic or myelomonocytic
- \textit{11q23 (MLL) balanced translocations most common}
- Occasionally ALL with t(4;11)
- Poor prognosis
Promyelocytic Leukemia with t(V;17)

- Morphologic features of PML or intermediate to PML and AML with maturation
- Translocation may involve RAR\(\alpha\) gene on 17 but not the PML gene
- t(11;17) and t(5;17) are two examples
- DIC is common
- Most fail on ATRA therapy; t(5;17) is an exception
- Unfavorable to intermediate prognosis
AML With Recurrent Genetic Abnormalities (Provisional)

- AML With Mutated NPM1
- AML With Mutated CEBPA
Rationale For The WHO Classification Of Myeloid Neoplasms

- Incorporates morphologic, immunophenotypic, genetic and clinical features to define entities that are biologically homogeneous and have clinical relevance.