Classifying Hematopoietic Disorders

French-American-British (FAB)
World Health Organization (WHO)

Thanks to:
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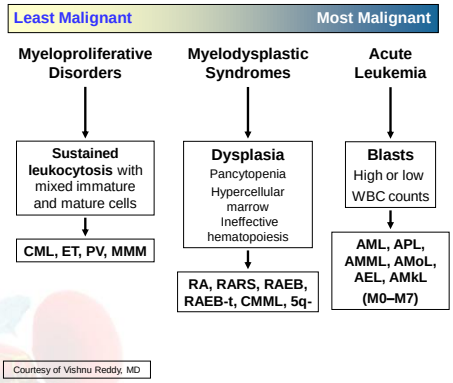
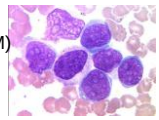
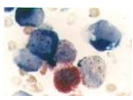


Courtesy of Vishnu Reddy, MD

FAB Classification Begun in 1976

- Based on Wright-stain peripheral blood (PB) and bone marrow (BM) morphology
- Cytochemistry: special dyes
  - Myeloperoxidase &Sudan black B
  - Esterase : specific and non-specific
- Cytogenetics: Ph' chromosome
  - Balanced reciprocal translocation t(9,22)(q34;q11.2)



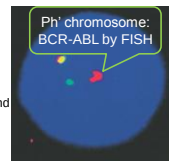


Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the acute leukaemias. Br J Haematol 1976;33:451-8.

Developments of the 1990s

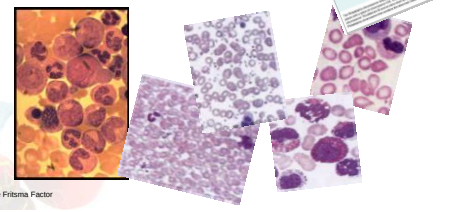
- FAB classification becomes confounded as technology develops
  - Phenotyping by flow cytometry: lymphomas, acute and chronic lymphocytic leukemia
  - Karyotyping extended: for example, t(15,17), 5q-
  - Fluorescent in situ hybridization (FISH)
- WHO initiates 1995 meeting of…
  - The European Association of Pathologists
  - the International Society for Hematopathology

Harris NL, Jaffe ES, Diebold J, et al. The WHO classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting. Hematol J 2000;1:53–66



Myeloproliferative Disorders (MPDs) Myeloproliferative Neoplasms

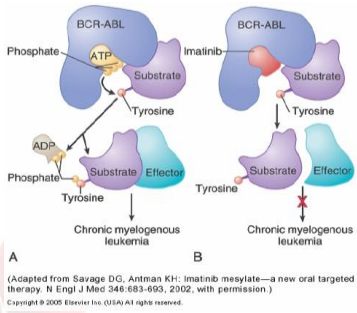
- FAB: based on Wright-stain BM morphology
  - Chronic myelogenous leukemia (CML) with Ph'
    - CML with eosinophilia
  - Polycythemia vera (PV)
  - Essential thrombocythemia (ET)
  - Myelofibrosis with myeloid metaplasia (MMM)



Philadelphia Chromosome

- Juxtaposition of *c-abl* proto-oncogene (chrom 9) with portion of *bcr* gene (chrom 22) yields *BCR/ABL* fusion gene
- Produces 210-kD bcr/abl fusion protein with abnormal tyrosine kinase activity
  - Activates signal transduction pathways
  - Raises proliferation, suppresses apoptosis
- Occasional patients lack Ph' but show *BCR/ABL* rearrangement by PCR
- Occasionally found months before CML Dx

Abnormal Tyrosine Kinase



(Adapted from Savage DG, Antman KH: Imatinib mesylate—a new oral targeted therapy. N Engl J Med 346:683-693, 2002, with permission.)

World Health Organization (WHO)

- 2001: morphology, cytochemistry, immunophenotype, genetic and clinical features
- 2008 updates: molecular diagnosis
  - MPDs renamed *myeloproliferative neoplasms* (MPNs)
  - Indentified genetic abnormalities in pathogenesis of *BCR/ABL*-negative MPNs
  - Clonal abnormalities of genes that encode cytoplasmic or membrane receptor *tyrosine kinases* that activate signal transduction pathways to cause proliferation
  - *Histologic* features: megakaryocytic localization, marrow stromal changes, multiple cell lineages involved in proliferation used as criteria to identify subtypes
  - Correlation with clinical features

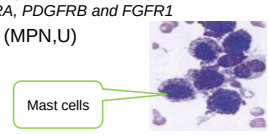
Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the WHO classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009 Apr 8. [Epub ahead of print accessed 6-19-09]

MPN: Molecular Characteristics Beyond BCR/ABL

- *JAK2*: Janus 2 kinase
  - Most common mutation at 9p24: *JAK2* V617F
- Platelet derived growth factor receptor-α (PDGFRA)
- Platelet derived growth factor receptor-β (PDGFB)
- FGF1: Fibroblast growth factor 1

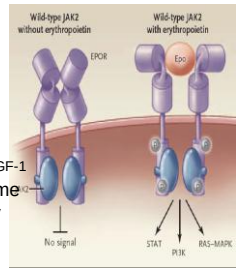
WHO Classification of MPNs

- CML, *BCR-ABL* positive
- Chronic neutrophilic leukemia (CNL)
  - *BCR-ABL* negative
- PV: 90% *JAK2* V617F positive
- Primary myelofibrosis (MMM, PMF); 50% *JAK2* Pos
- ET; PLT count threshold now ≥450,000/uL; 50% *JAK2* Pos
- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA, PDGFRB and FGFR1*
- MPN, unclassifiable (MPN,U)
- Mastocytosis



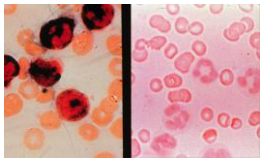
Polycythemia Vera

- HGB
  - Males >18.5 g/dL
  - Females >16.5 g/dL
- *JAK2* V617F
- Progenitor cells hyper-sensitive to cytokines
  - Erythropoietin
  - SCF, GM-CSF, IL-3, TPO, IGF-1
- In PMF and ET, also some cytokine hypersensitivity



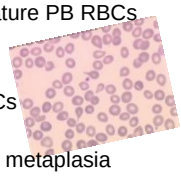
Chronic Neutrophilic Leukemia

- No Ph' chromosome
- WBC > 25,000/uL
  - Mature neutrophils predominate
  - No evidence of infection
- Leukocyte alkaline phosphatase ↑, not ↓
- Slowly progressive



Primary Myelofibrosis (PMF)

- MOD/MKD reactive marrow fibrosis
- Myeloid metaplasia: hepatosplenomegaly
- Leukoerythroblastic: Immature PB RBCs and neutrophils
- WBC <30,000/mL
- N/N anemia: teardrop RBCs
- FAB names: Agnogenic myelofibrosis with myeloid metaplasia (AMMM, MMM)
- WHO 2001 name: Chronic idiopathic myelofibrosis (IMF)

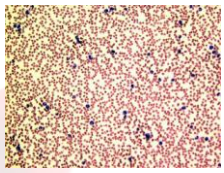


PMF Diagnosis: WHO 2008 Major Criteria: Must meet all three

1. Megakaryocyte (MK) atypical proliferation
   - With either reticulin or collagen fibrosis
   - In the absence of fibrosis, MK changes must be accompanied by ↑ BM cellularity with myelocytic proliferation and ↓ erythropoiesis
2. *JAK2* (50% of patients) or other clonal marker such as *MPL* W515K/L
   - If no clonal marker, BM fibrosis cannot be secondary to infection, autoimmune disorder or other chronic inflammatory condition, lymphoid neoplasm or metastatic malignancy
3. Exclude WHO criteria for PV, *BCR-ABL* CML, MDS or other myeloid neoplasms

PMF Diagnosis: WHO 2008 Minor Criteria: Must meet two

- Leukoerythroblastosis
- Raised serum lactic dehydrogenase
- Anemia
- Splenomegaly

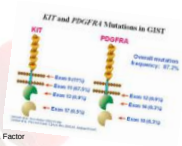


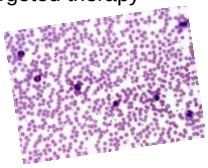
ET: WHO 2008 Criteria

1. Sustained PLT count ≥450,000/uL
   - Reduced from ≥ 600,000/uL in 2001
2. BM biopsy: massive megakaryocytic proliferation
   - No left-shift or significant increase of myelopoiesis or erythropoiesis
3. *JAK2* 50%, or other clonal marker
   - In absence of *JAK2*, must show no evidence for reactive thrombocytosis
4. Exclude WHO criteria for PV, *BCR-ABL* CML, MDS or other myeloid neoplasms

Myelogenous or Lymphoid Neoplasms with Eosinophilia & Abnormalities of PDGFRA, PDGFRB or FGFR1

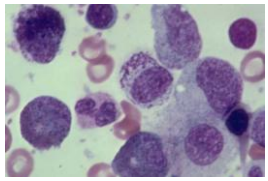
- Three rare specific disease groups
- All result from a fusion gene that encodes aberrant tyrosine kinase activity
- Eosinophilia characteristic, not invariable
- Important to recognize since tyrosine kinase inhibitors are targeted therapy





Mastocytosis

- Clonal proliferation of mast cells that accumulate in one or more organ systems
- Multifocal compact clusters or cohesive aggregates of abnormal mast cells
- Same as WHO 2001, except now included in MPN



MPN-Unclassifiable

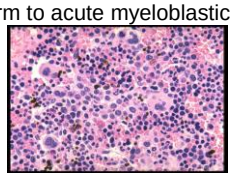
- Definite clinical, and laboratory features of MPN, but fail to meet criteria for any of the specific MPN entities
- MPN that presents with features overlapping or more of the MPN
- May be early stages of PV, PMF or ET in which features are not yet developed
- May be advanced MPN
  - Multiple, combined, or co-existing neoplastic or inflammatory disorder that obscures MPN Dx features

Myelodysplastic/Myeloproliferative Neoplasms

- Clonal myeloid disorders that possess both dysplastic and proliferative features that are not classified as either MDS or MPN
- Atypical (aCML): *BCR/ABL* negative
- Chronic myelomonocytic leukemia (CMML)
- Juvenile myelomonocytic leukemia (JMML)
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable

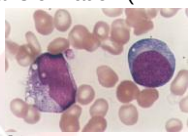
Myelodysplastic Syndromes (MDS)

- Abnormal myeloblastic clones mixed with normal maturation
  - Altered, unbalanced gene functions
- Variable anemia and cytopenia, may smolder for years
  - Some are transfusion dependent
- 20–40% transform to acute myeloblastic leukemia



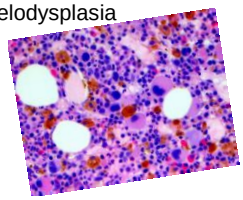
MDS FAB Classification

- Refractory anemia (RA)
- Refractory anemia with ringed sideroblasts (RARS)
- Refractory anemia with excess blasts (RAEB)
- Refractory anemia with excess blasts in transformation (RAEB-t)



MDS: WHO 2001

- Refractory anemia with or without ringed sideroblasts
- Refractory pancytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Unclassified myelodysplasia
- 5q- syndrome



Significant MDS Differences FAB and WHO 2001

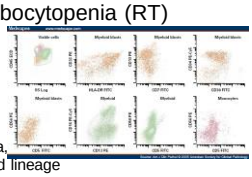
- RAEB-t eliminated
- RA and RARS have *unilineage* dysplasia: only dyserythropoiesis
- Refractory cytopenia with multilineage dysplasia (RCMD) added
- MDS with del (5q) as sole genetic abnormality added as 5q- syndrome
- Therapy-related MDS/AML grouped as a single syndrome
- CMML moved to MDS/MPN category

MDS: 2008 WHO Updates

- Refractory cytopenia with unilineage dysplasia (RCUD, 2008)
- Refractory anemia with or without ringed sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- RAEB-1 (<5% blasts, no Auer rods)
- RAEB-2 (5-19% blasts, Auer rods)
- MDS-U
- MDS with isolated del (5q), (5q-)
- Childhood MDS (2008)

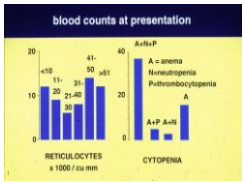
RCUD

- Refractory anemia (RA)
- Refractory neutropenia (RN)
- Refractory thrombocytopenia (RT)
- Peripheral blood
  - Unicytopenia
  - No or <1% blasts
- Bone marrow
  - Unilineage dysplasia, >10% in one myeloid lineage
  - < 5% blasts
  - < 15% ring sideroblasts



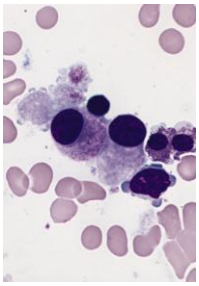
RCMD

- Bicytopenia or pancytopenia with dysplasia in 10% of two or more cell lines
  - <1% blasts in PB
  - <5% blasts in BM
  - No Auer rods
- 50% have karyotypic abnormalities
  - Monosomy 5
  - Del (5q)
  - Monosomy 7
  - Del (7q)
  - Trisomy 8
  - Del (20q)



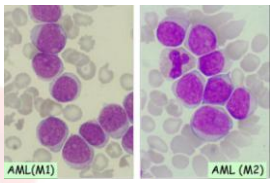
5q- Syndrome

- Deletion 5q ($5q^{-32-33.3}$) is sole abnormality
- Macrocytic anemia with otherwise normal blood counts
- Blasts in marrow <5%
- Hypolobulated megakaryocytes
- Normal or high platelets
- Male: female ratio 1:3
- Favorable: low progression to AML



Acute Myeloblastic Leukemia (AML)

- Neoplastic cells escape apoptosis resulting in expansion of leukemic clone
- Failure to differentiate into functional hematopoietic cells
- Proliferate and accumulate in BM



FAB Acute Myeloblastic Leukemia

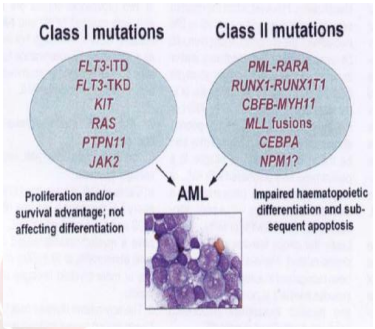
FAB	Name	Phenotype	Image
M0	AML, minimally differentiated	CD13, 33, 34,117	
M1	AML without differentiation		
M2	AML with differentiation		
M3	Acute promyelocytic (APL)	Genotype: t(15;17)	
M4	Acute myelomonocytic (AMML)	CD4, 11c, 13, 14, 33, 36, 64	
M5	Acute monoblastic (AMoL)	CD4, 11b, 13, 14, 36, 64	
M6	Acute erythroid leukemia	CD11b, 13, 15, 33, 34, 45, 71	
M7	Acute megakaryocytic	CD 41, 42, 61	

AML With Recurrent Translocations

- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML/RARA*
- AML with t(9,11)(q22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*

The last 3 are defined in 2008.

Multi-stage Theory Proliferation + Survival



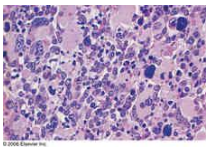
AML With MDS-related Changes*

- Category has ≥ 20% PB or BM blasts
- *And* any of following:
  - Prior history of MDS
  - MDS-related cytogenetic abnormality
  - Multilineage dysplasia
- *And* absence of…
  - Prior cytotoxic therapy for an unrelated diagnosis.
  - Recurring genetic abnormality.
- For prognosis, monitor for *FLT3, NPM1, and CEBPA*

*This category replaces 2001 "AML with multilineage dysplasia."

Therapy-related Myeloid Neoplasms

- Uncommon consequence of mutations induced by cytotoxic therapy:
  - Alkylating agents
  - Ionizing radiation
  - Topoisomerase II inhibitors
  - Others: antimetabolites, antitubulin agents
- Despite similar mutations, worse outcomes in…
  - t-AML
  - t-MDS
  - t-AML/t-MDS
  - t-MDS/MPN
  - t-AML/t-MDS/MPN



AML Not Otherwise Specified*

- AML without maturation
- AML with minimal differentiation
- AML with maturation
- Acute myelomonocytic leukemia (AMML)
- Acute monoblastic/monocytic leukemia (AMoL)
- Acute erythroid leukemia (AEL)
  - Erythroleukemia, erythroid/myeloid
  - Pure erythroid leukemia
- Acute megakaryoblastic leukemia (AMkL)
- Acute basophilic leukemia (ABL)
- Acute panmyelosis with myelofibrosis

*Do not fill criteria for any other AML categories, follow FAB classification.

Two 2008 Additions

- Myeloid proliferations related to Down syndrome
  - MDS and AML are identical in Down syndrome
- Blastic plasmacytic dendritic cell neoplasm
  - Formerly blastic NK-cell lymphoma/leukemia, CD4, 56

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Acute Leukemias of Ambiguous Lineage

- Acute undifferentiated leukemia: no lineage-specific markers
- Mixed phenotype AL with t(9;22)(q34;q11.2); *BCR-ABL*
- Mixed phenotype AL with t(v;11q23); MLL rearranged
  - B/myeloid not otherwise specified
  - T/myeloid, not otherwise specified

The Fritsma Factor

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Lymphoblastic Leukemia

- B-lymphoblastic leukemia/lymphoma, not otherwise specified
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - t(9:22)(q34;q11.2) *BCR-ABL*
  - t(v;11q23), *MLL rearranged*
  - t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1*)
  - Hyperdiploidy, hypodiploidy
  - t(5;14)(q31;q32) *IL3-IGH*
  - t(1;19)(q23;p13.3) *TCF3-PBX1*
- T-lymphoblastic lymphoma

The Fritsma Factor