Update:
Acute Myeloid Leukemia and the WHO Classification

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DEPARTMENT OF MEDICAL LABORATORY SCIENCES

Objectives

- Discuss major features of the **W**orld **H**ealth **O**rganization Classification of **A**cute **M**yeloid **L**eukemia
- Review laboratory testing essential to the diagnosis and treatment of AML
- Discuss case studies of several different types of AML
- Review some targeted therapies for AML

Leukemia

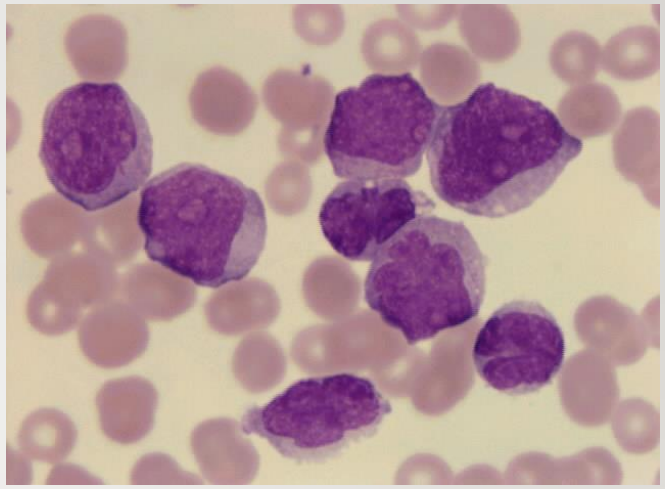
- Progressive, malignant disease of the blood forming organs
- Unregulated proliferation and development of leukocytes and their precursors in the bone marrow
- Malignant cells spill over into the peripheral blood

Classification of Leukemias

- Cell maturity
- Cell lineage

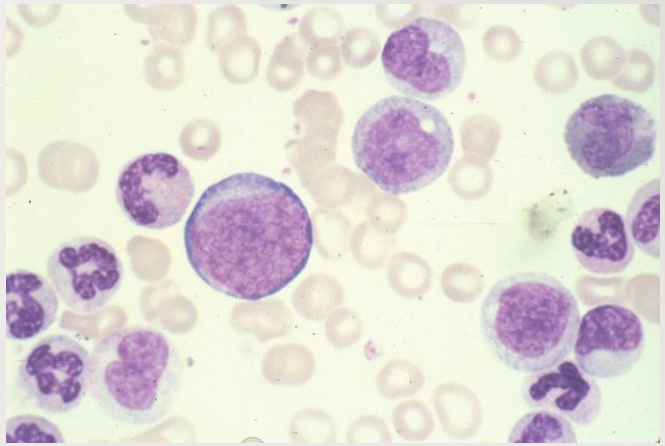
Cell Maturity

- Acute – predominance of immature cells



vs

- Chronic – more differentiated/mature cells

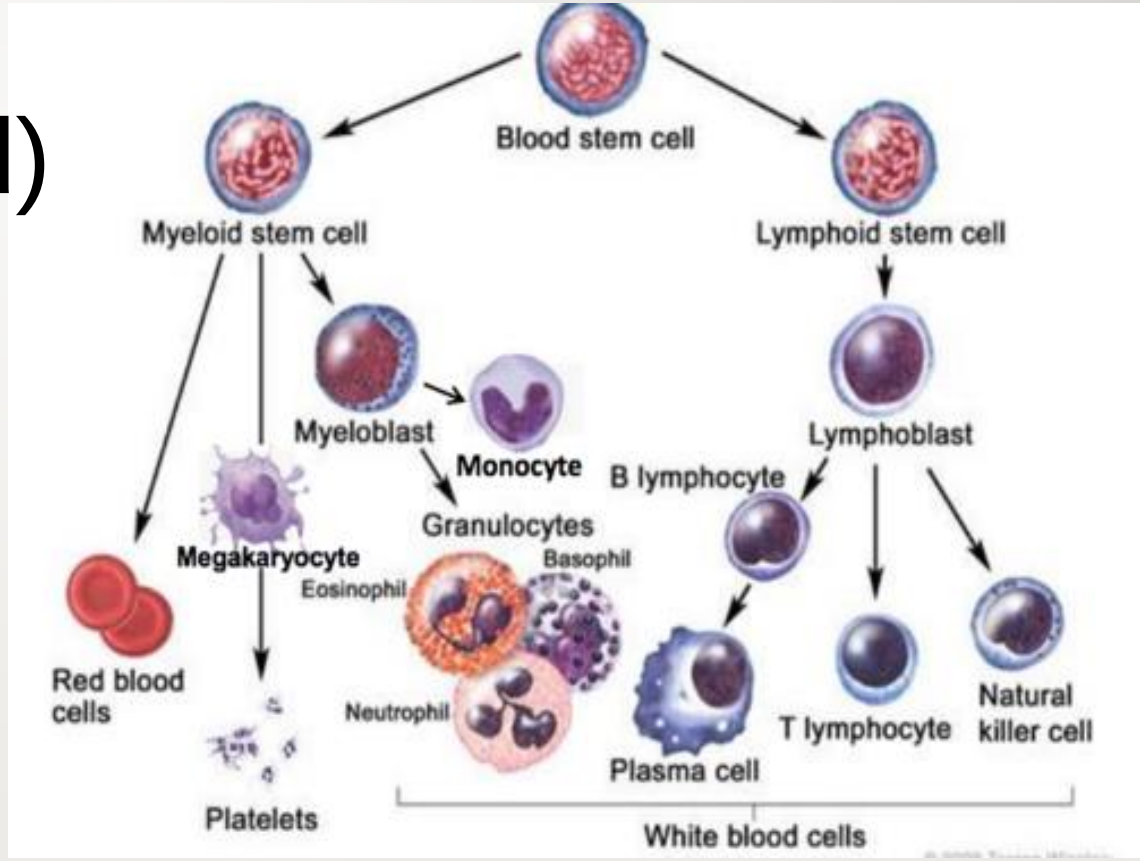


Cell Lineage

Myeloid (Non-lymphoid)

vs

Lymphoid



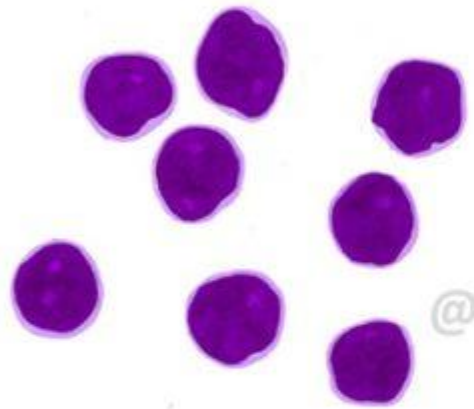
FAB Classification of Acute Leukemias

- Proposed in1976
  - 7 hematologists
    - French, American, British
  - 2 groups of acute leukemias
    - Lymphoid
    - Myeloid
  - Based on **morphology** and **cytochemistry**

FAB Classification of Acute Lymphoblastic Leukemias (ALL)

	L1	L2	L3
Cell size	Small	Large, often heterogeneous	Large, homogeneous
Amount of cytoplasm	Scant	Moderately abundant	Moderately abundant
Nucleoli	Inconspicuous	Prominent	Present, may be prominent
Cytoplasmic vacuoles	Variable	Variable	Prominent

ALL-L1

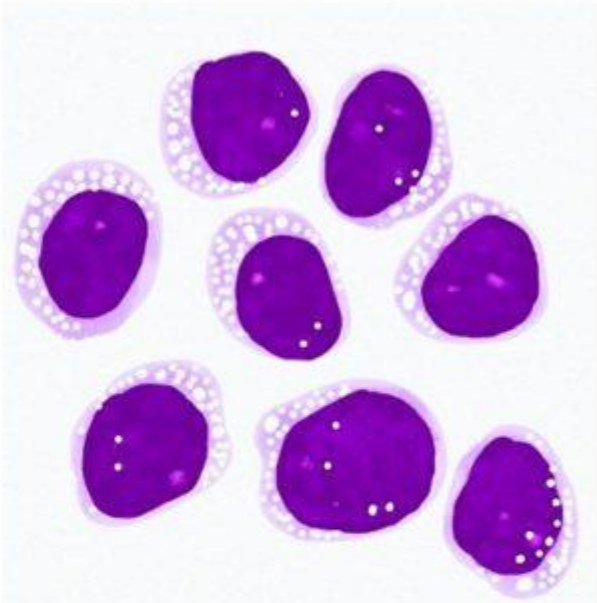


Small uniform cells. Nuclei regular with condensed chromatin, inconspicuous nucleoli. Scant cytoplasm

ALL-L2

Large, heterogenous cell population. Nuclei irregular/clefting with occasional nucleoli. Mild to moderate cytoplasm

ALL-L3



Large, homogeneous cell population. Nuclei regular with fine chromatin and 1-2 nucleoli.Moderate to abundant vacuolated cytoplasm

WHO Classification of Acute Lymphoblastic Leukemia/Lymphoma

Type of lymphoblast	WHO subtype
Precursor B cell	B lymphoblastic leukemia/lymphoma, not otherwise specified, NOS
Precursor B cell	B lymphoblastic leukemia/lymphoma with recurrent cytogenetic abnormalities: •with t(9;22) •with t(v;11q23) •with t(12;21) •with hyperdiploidy (more than 50 chromosomes) •with hypodiploidy (less than 50 chromosomes) •with t(5;14) •with t(1;19)
Precursor T cell	T lymphoblastic leukemia/lymphoma

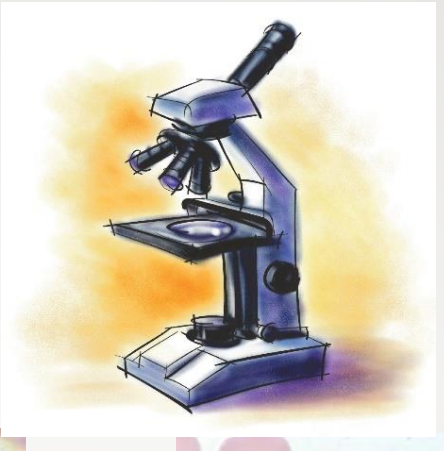
FAB classification of Acute Myeloid Leukemia (AML)

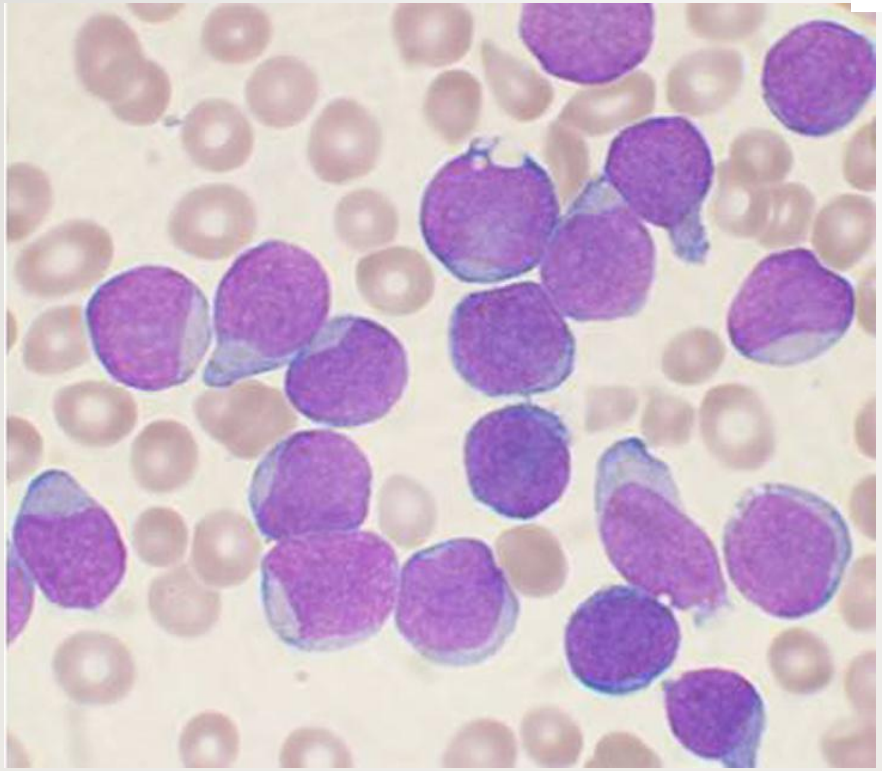
- Divided into 6 categories
  - M1 – M6
  - Later added M0 and M7 (1991)

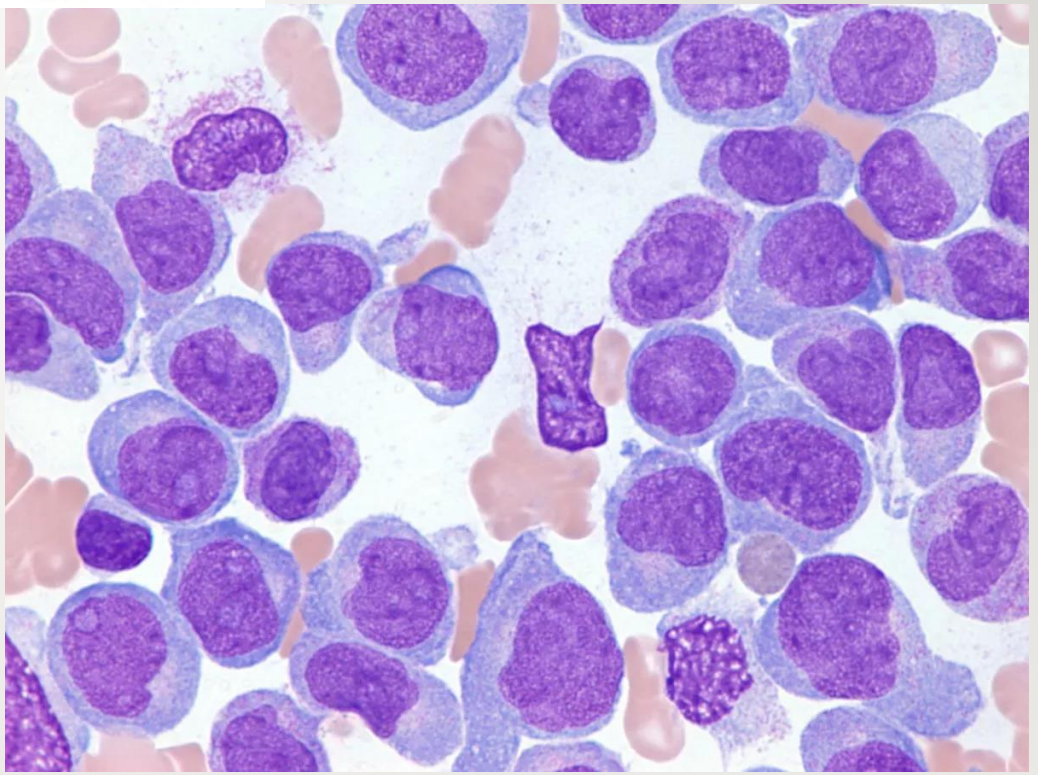
FAB Classification of AML

- M0 – AML with minimal differentiation
  - Blasts don't express many markers of myeloid differentiation, including MPO
- M1 – AML without maturation
  - At least small subset of blasts express markers of myeloid differentiation (MPO)
- M2 – AML with maturation
  - AML with t(8;21) falls within this category
- M3 – Acute promyelocytic leukemia
  - AML with t(15;17); myeloblasts and promyelocytes (blast equivalents)
- M4 – Acute myelomonocytic leukemia
  - Myeloblasts and monoblasts (blast equivalents)
  - M4eo = AML with inv(16); favorable prognosis
- M5 – Acute monoblastic/monocytic leukemia
- M6 – Erythroleukemia
  - Myeloblastic and/or erythroblastic proliferation
- M7 – Acute megakaryoblastic leukemia
  - Associated with Down Syndrome

Morphology

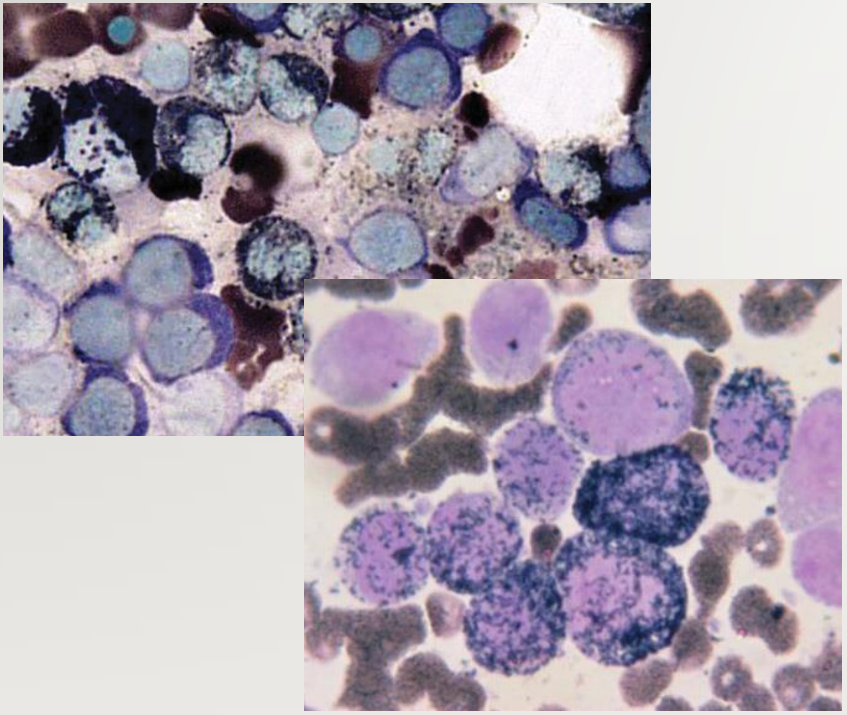






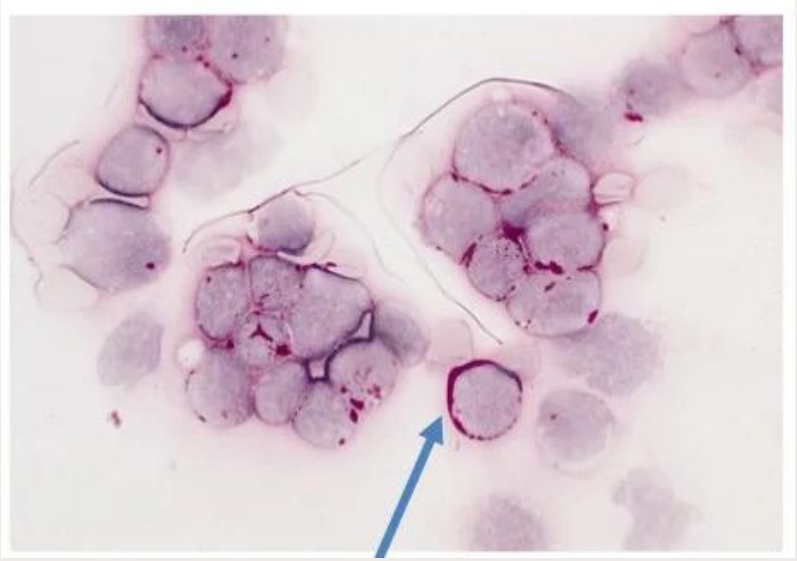
Cytochemistry

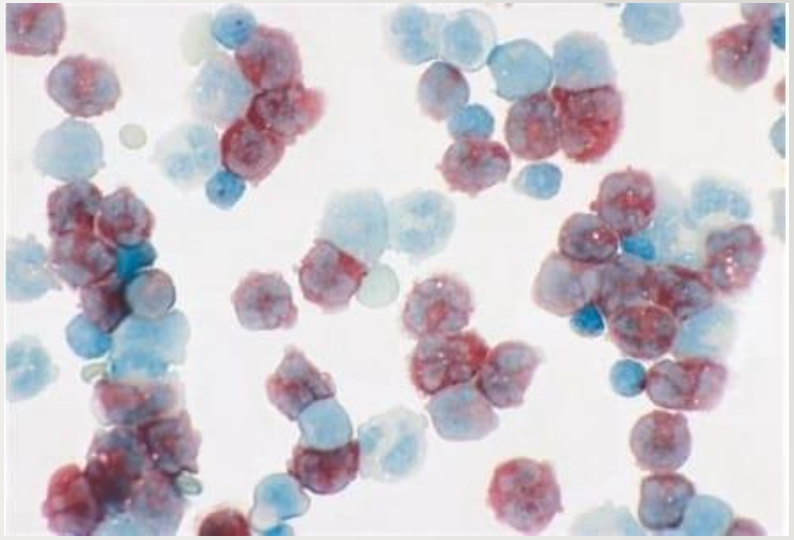
SBB/ MPO, PAS, Esterases (specific and non specific)



Sudan Black/MPO – myeloid lineage

Periodic Acid Schiff –
lymphoid lineage



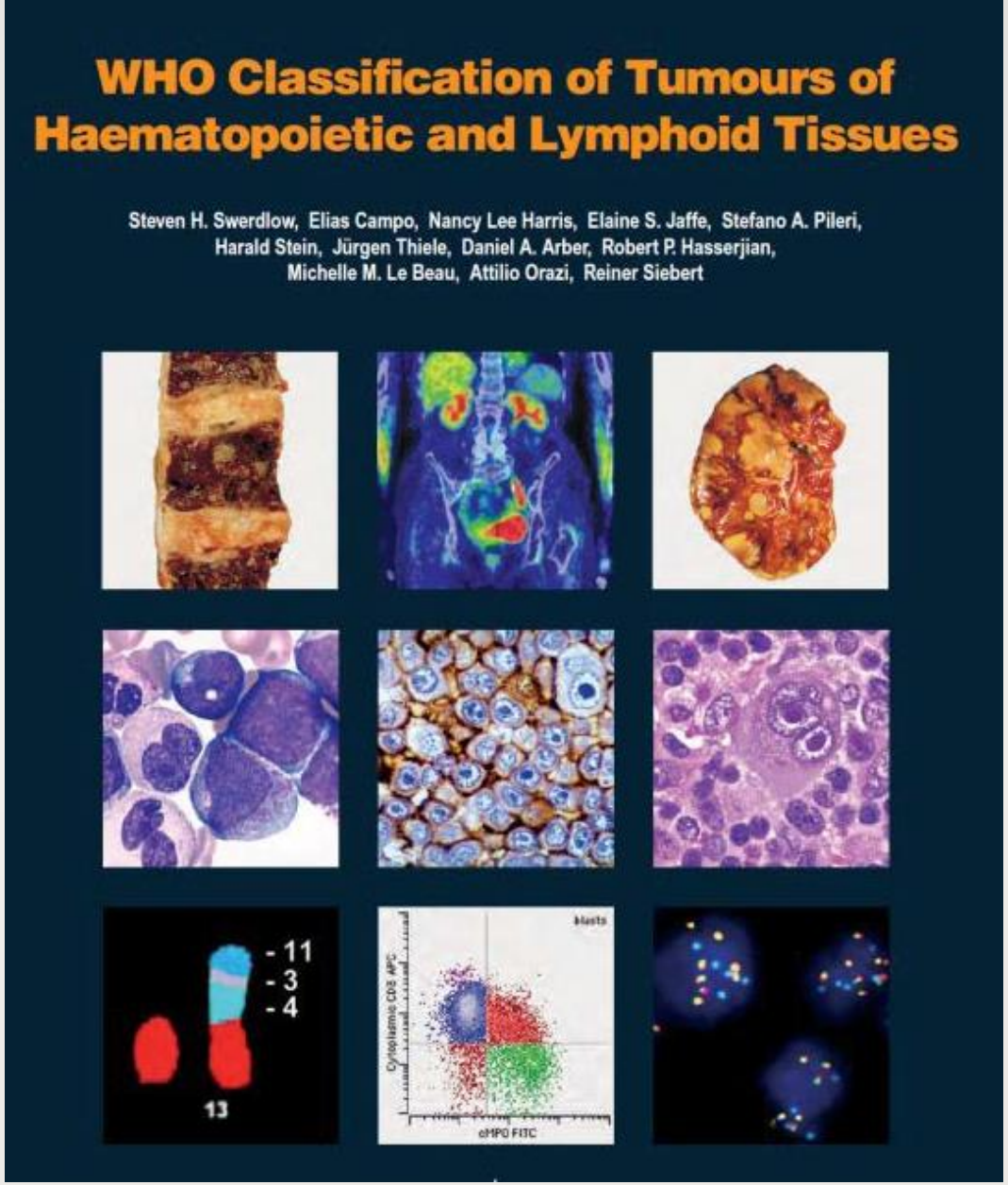


Non specific esterase –
granulocytic vs monocytic lineage

WHO Classification of Tumors of Hematopoetic and Lymphoid Tissue

- First published in 2001
- First true worldwide collaboration
- Extended to include all hematopoetic and lymphoid tumors

Updated in 2008, 2017



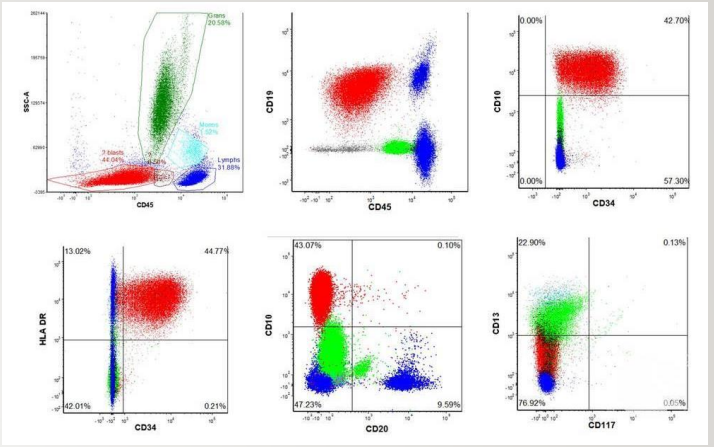
2017 edition

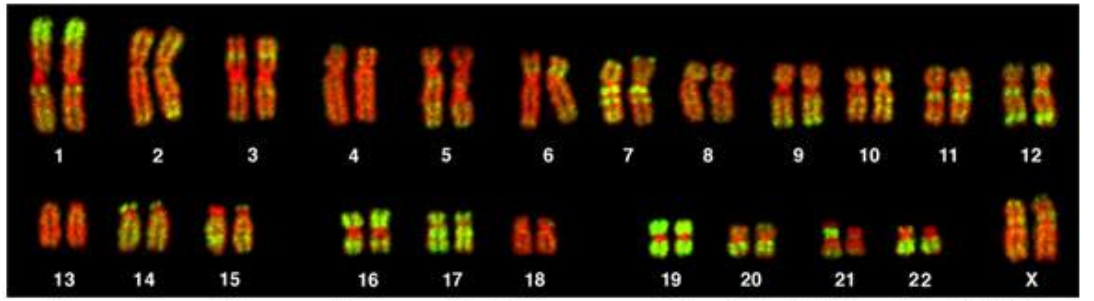
Blast % in Blood and/or Bone Marrow that defines an Acute Leukemia

- FAB - 30% or >
- WHO - 20% or >
  - Based on morphologic differential cell count (not flow)
- Few exceptions
  - “Blast equivalents” – e.g.
    - Promyelocytes (only in Acute Promyelocytic Leukemia)
    - Promonocytes

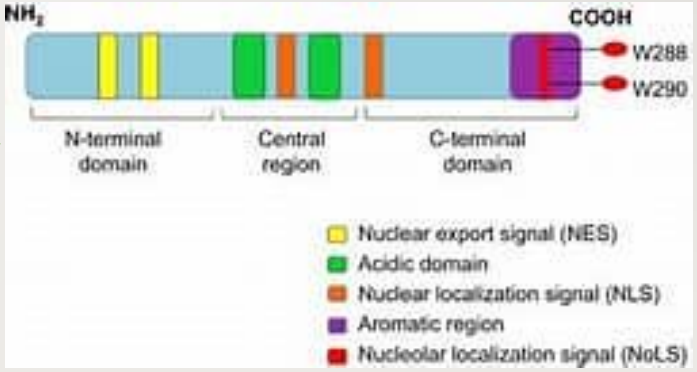
WHO Classification Criteria

- ***Morphology***
- ***Cytochemistry***
- **Immunophenotyping**
- **Cytogenetics/FISH**
- **Molecular Diagnostics**
- **Clinical history**
  - **Prior myeloid neoplasm, chemo and/or radiotherapy**



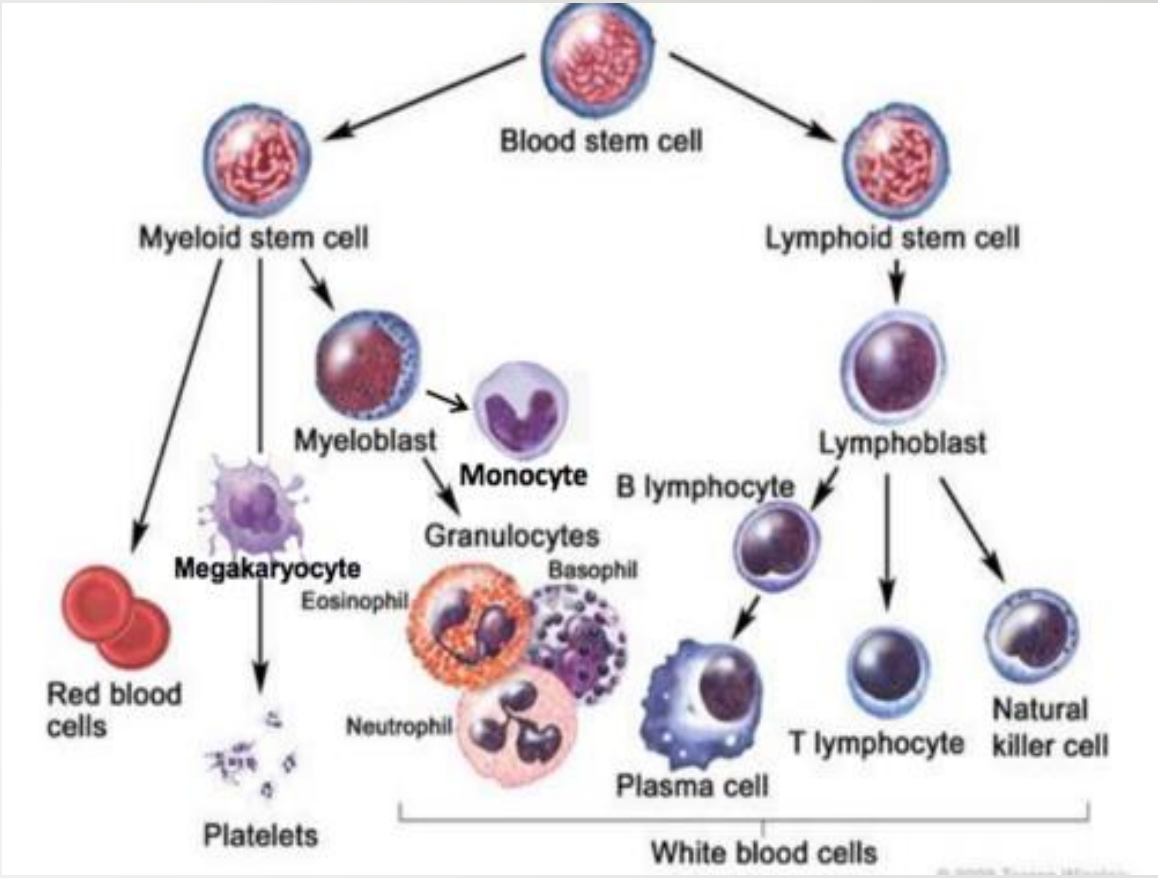


Karyotype of Human Prepared by Fluorescence *in situ* hybridization (FISH)



Immunophenotyping

- Myeloid markers
  - CD33, CD13, CD14, CD64, MPO
- T cell markers
  - CD3, CD4, CD5, CD7, CD8
- B cell markers
  - CD19, CD20, CD22, CD79a
- Markers of immaturity
  - CD34, CD117, TdT



Note: Neoplastic populations do not always follow the rules! Leukemic cells may express antigens typically associated with other lineages

Cytogenetics/Molecular Mutations

- **Translocations**
  - Unregulated overexpression of a proto-oncogene
  - Creation of an novel fusion gene
- **Point mutations**
  - Increased function of a proto-oncogene
  - Decreased function of a tumor suppressor gene
- **Deletions**
  - Decreased effect of tumor suppressor gene

Proto-oncogene

- Normal gene that codes for a particular protein involved in cell division
- Responsible for regulation of cell division
- May also regulate apoptosis
- When mutated – may transform into oncogene which has the potential to cause cancer
- Acquired somatic mutations

Tumor suppressor gene

- Normal gene – also called anti-oncogene
- Functions include
  - Slowing down cell cycle – suppress cell division when necessary
  - Marking cells for apoptosis
  - DNA repair
- May be acquired somatic cell mutation
- May also be present in germ cell (inherited)
  - e.g. P53 (molecular policeman or guardian of the genome)
    - Regulates cell cycle
    - Detect DNA damage and activate DNA repair proteins
    - Increased risk of certain types of cancer

WHO Classification of Acute Myeloid Leukemias 2017

1. AML with recurrent genetic abnormalities

AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1* ***(FAB M2)***

AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11* ***(FAB M4Eos)***

APL with t(15;17)*PML-RARA* ***(FAB M3)***

AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A* ***(FAB M5)***

AML with t(6;9)(p23;q34.1);*DEK-NUP214*

AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*

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

AML with mutated NPM1

AML with biallelic mutations of CEBPA

Provisional entity: AML with BCR-ABL1

Provisional entity: AML with mutated RUNX1

2. AML with myelodysplasia-related changes

3. Therapy-related myeloid neoplasms

4. AML, NOS

AML with minimal differentiation - **M0**

AML without maturation - **M1**

AML with maturation - **M2**

Acute myelomonocytic leukemia - **M4**

Acute monoblastic/monocytic leukemia - **M5**

Pure erythroid leukemia - **M6**

Acute megakaryoblastic leukemia - **M7**

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

5. Myeloid sarcoma

6. Myeloid proliferations related to Down syndrome

AML with recurrent genetic abnormalities

- 20 – 30% of all AMLs
- Balanced translocations
  - Two chromosomes exchange material when both break
- Include mutations in
  - Proto-oncogenes (become oncogenes)
  - Tumor suppressor genes (lose their suppressor function)
  - Other regulatory elements which control
    - Proliferation
    - Maturation
    - Apoptosis
    - Other cell functions

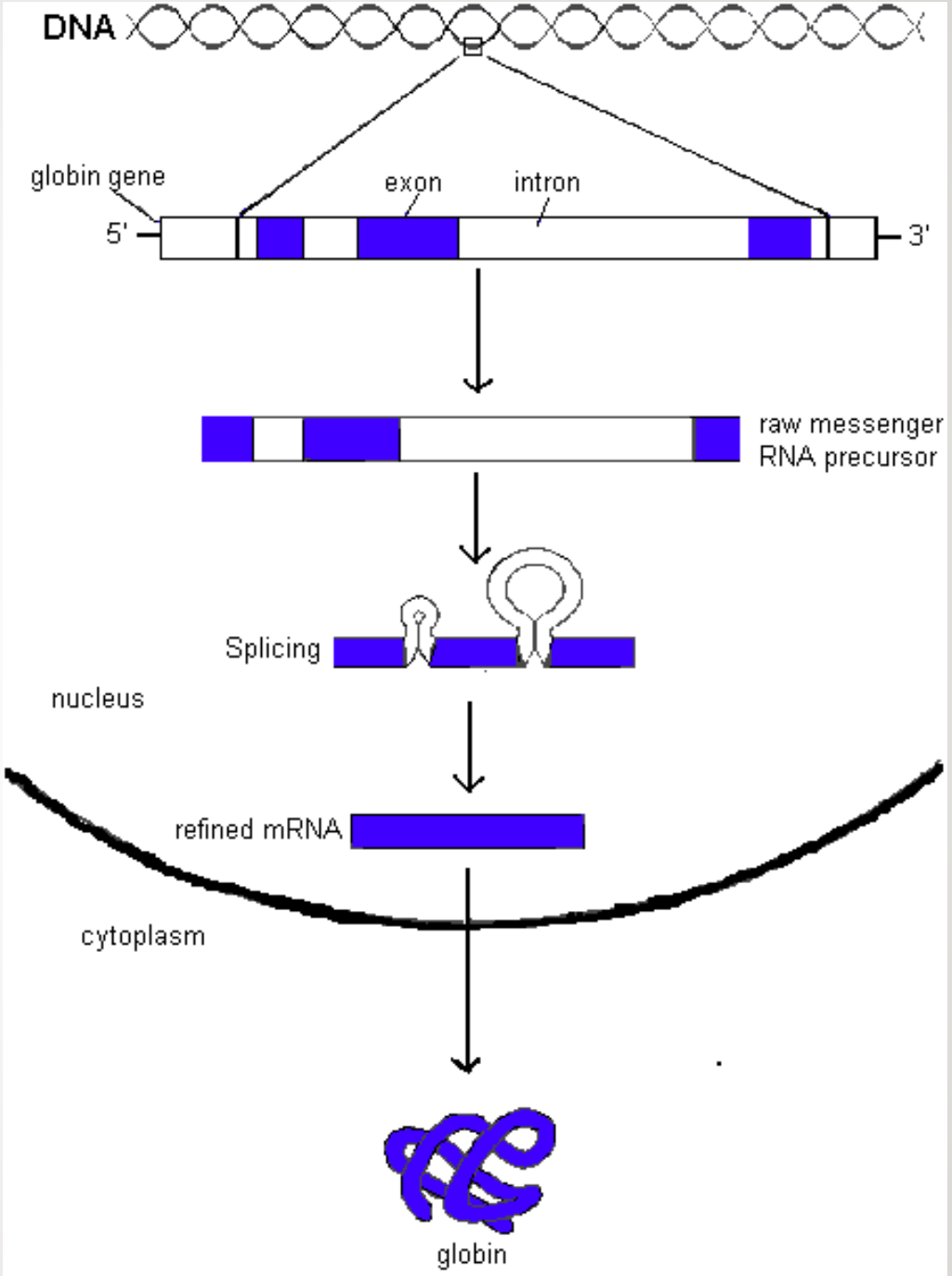
Protein Synthesis

Transcription

Processing

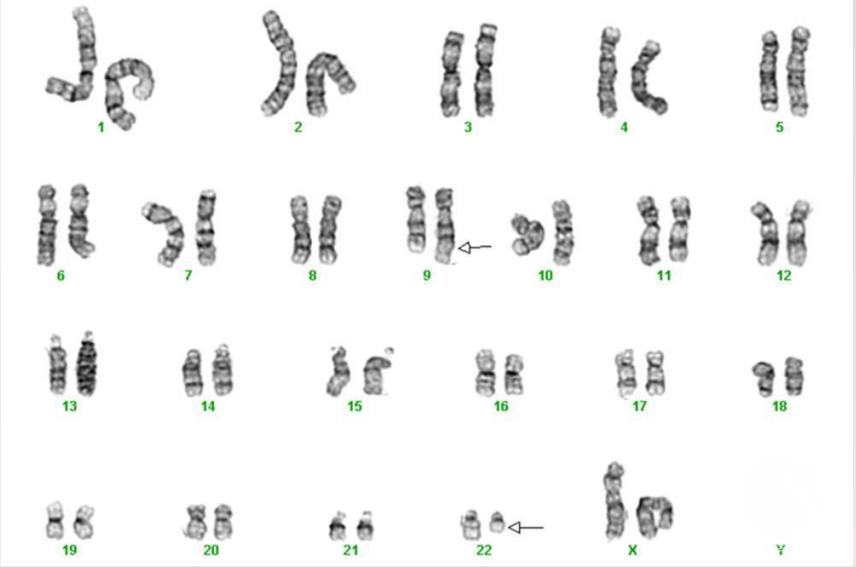
Transport

Translation

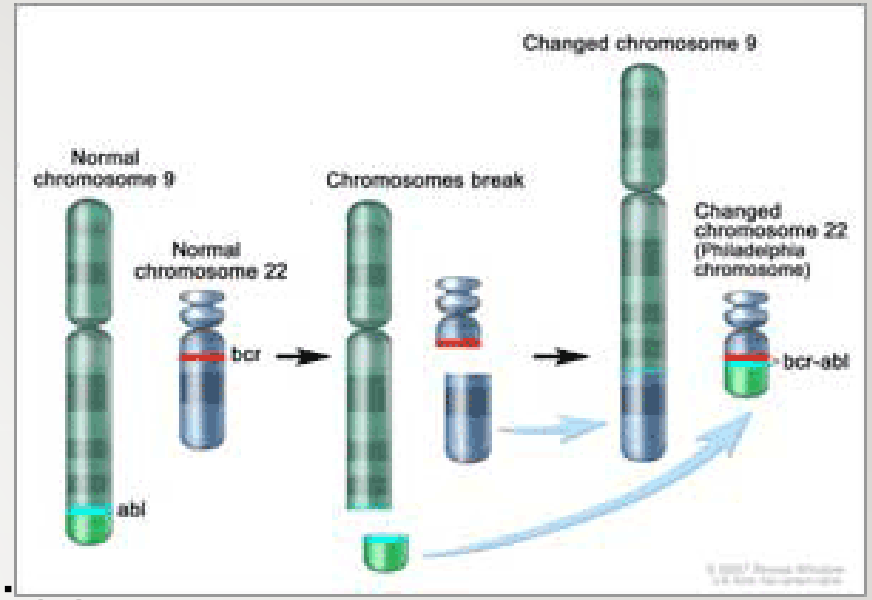


Philadelphia Chromosome

- Associated with Chronic Myelogenous Leukemia
- Discovered in 1959
- First clonal cytogenetic abnormality
- Balanced translocation
  - t(9;22)



BCR/ABL

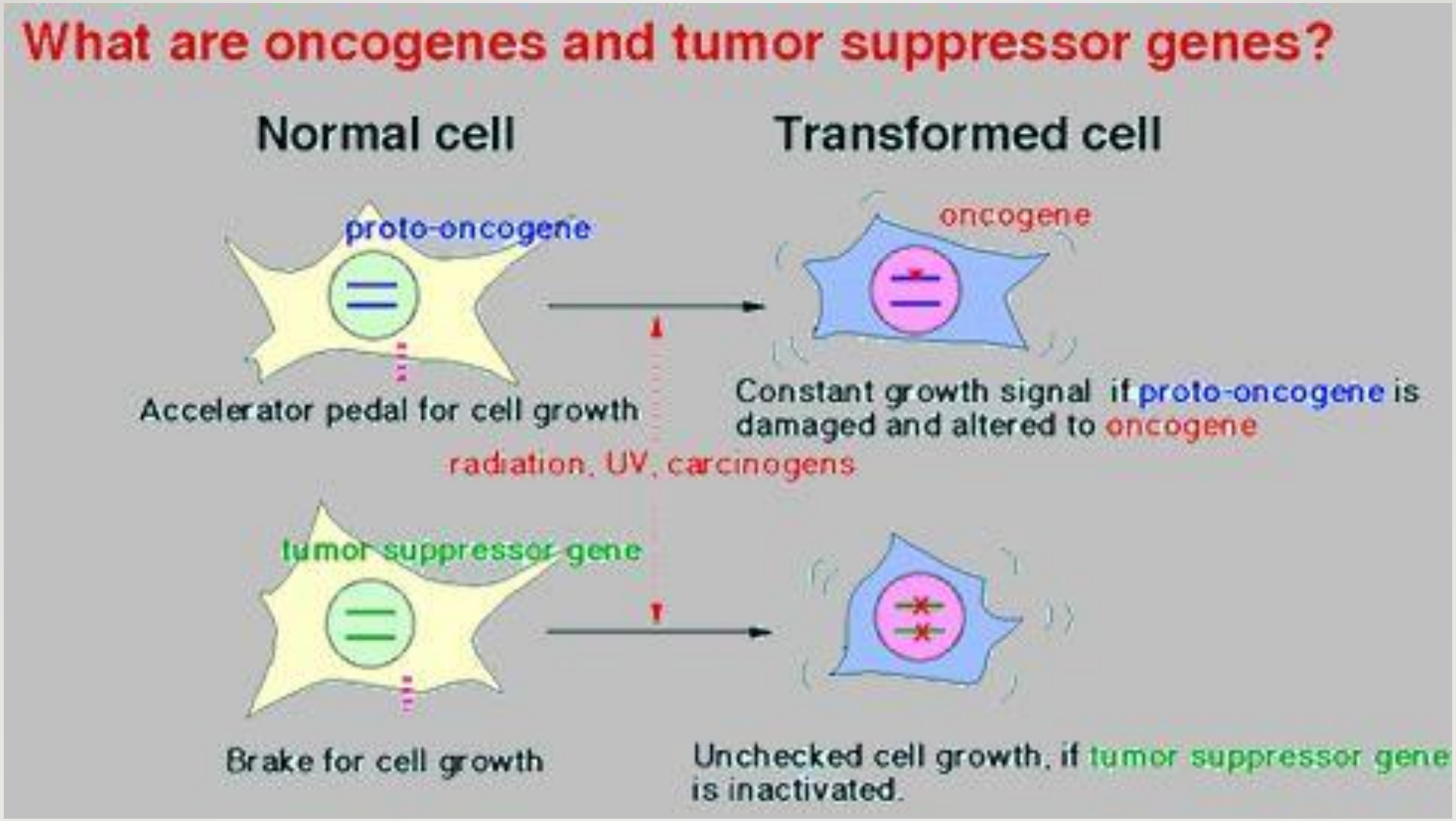


- Chimeric oncogene
- Results in production of abnormal tyrosine kinase
  - Enhanced enzyme activity
  - Uncontrolled proliferation of myeloid cells
  - Loss of apoptotic functions

Treatment for CML

- Targeted therapy FDA approved in 2001
- Gleevec (Imatinib mesylate)
- Inhibits abnormal tyrosine kinase produced by ABL/BCR fusion gene
- Revolutionized treatment for CML
  - ~90% 5 year survival rate among patients who consistently remained on therapy
- Newer generation TK inhibitors
  - Nilotinib and Dasatinib (2010)
  - Bosutinib (2015) and Ponatinib (2020)
  - Asciminib (10/2021)

What are oncogenes and tumor suppressor genes?



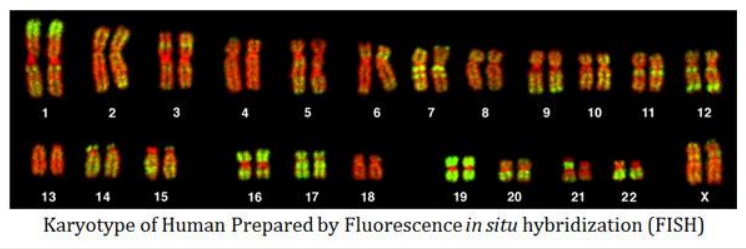
Getting back to WHO

- Why is this classification strategy so important?
  - Diagnosis
  - Treatment
  - Prognosis

AML required/key information for reporting

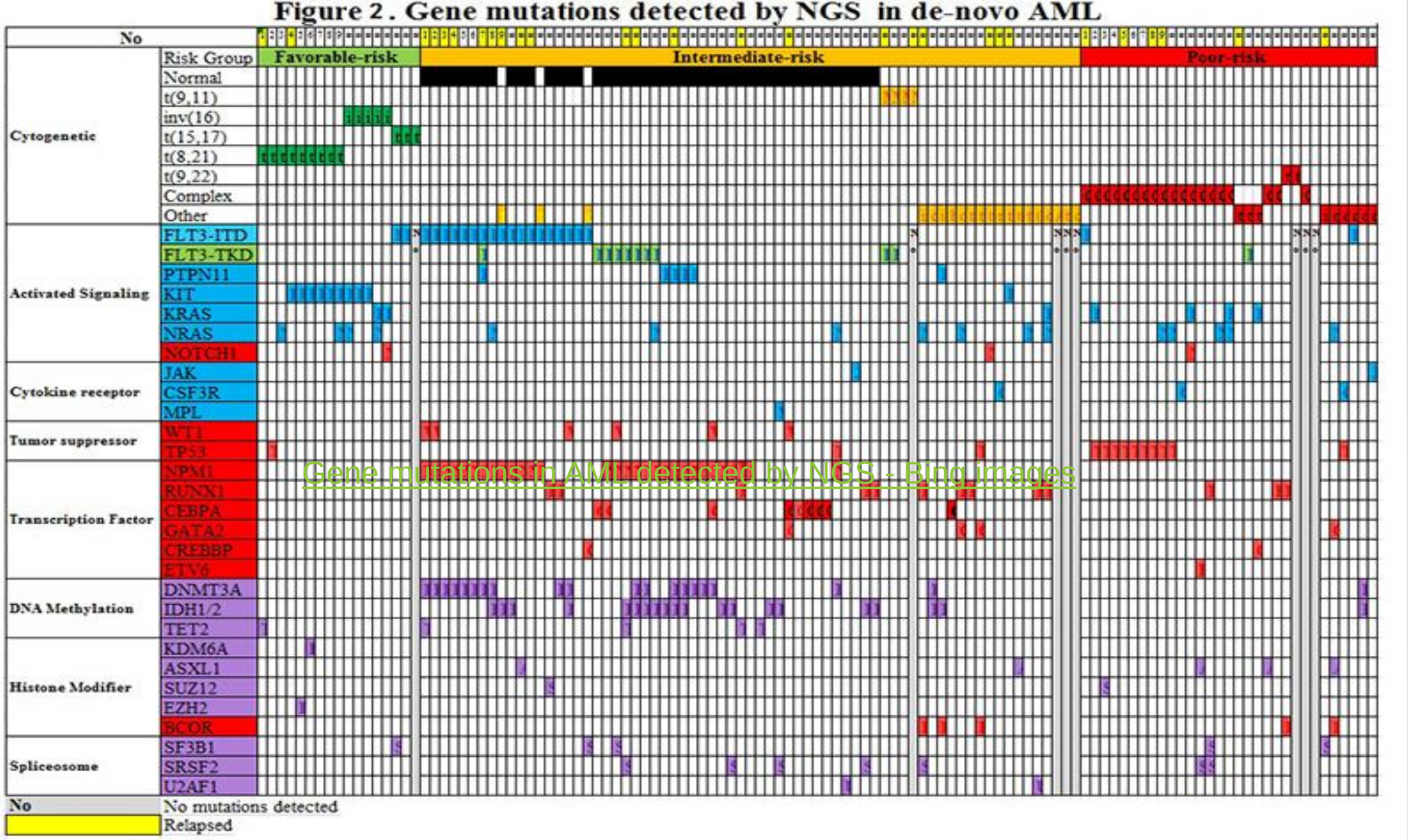
Clinical History:	History of chemo/radiation/MDS?
Morphology/Cytochemistry:	Blast %, Morphology, Dysplastic %, Cytochemistry +/-
Flow Cytometry: (all cases)	Confirm myeloid (CD33,CD13)
Cytogenetics: (all cases)	AML - defining vs other, + FISH
Molecular: (selected genes)	*FLT3, NPM1, CEBPA, RUNX1, BCR-ABL1, KIT, many* others

Genetic abnormalities in AML



Karyotype of Human Prepared by Fluorescence *in situ* hybridization (FISH)

- Molecular pathogenesis is complex
- Moving beyond cytogenetics/karyotyping
  - Major gene mutations discovered and identified using various high throughput sequencing technologies (e.g. NGS – Next Generation Sequencing)
  - Genetic data now being used in both diagnosis and prognosis in AML
  - Ever changing and evolving



Gene mutations in AML detected by NGS - Bing images

Author: Juan Ma, MD // **Date:** OCT.13.2015 // **Source:** Scientific Shorts

MAYO CLINIC LABORATORIES

Targeted Genes Interrogated by Next-Generation Sequencing, Acute Myeloid Leukemia, 11-Gene Panel

Genome Build GRCh37 (hg19)

Gene	GenBank Accession Number	Exons–Systematic Numbering
CEBPA	NM_004364.4	1
DNMT3A	NM_022552.4	8–23
FLT3	NM_004119.2	14–20
IDH1	NM_005896.3	4
IDH2	NM_002168.3	4
KIT	NM_000222.2	8–11 and 17
KRAS	NM_033360.3	3-Feb
NPM1	NM_002520.6	9–11, intron 10 30bp before exon 11
NRAS	NM_002524.4	2 and 3
RUNX1	NM_001001890.2	1–6, intron 4 c.725–13T>A and intron 5 c.886+1–4del
TP53	NM_000546.4	4–9

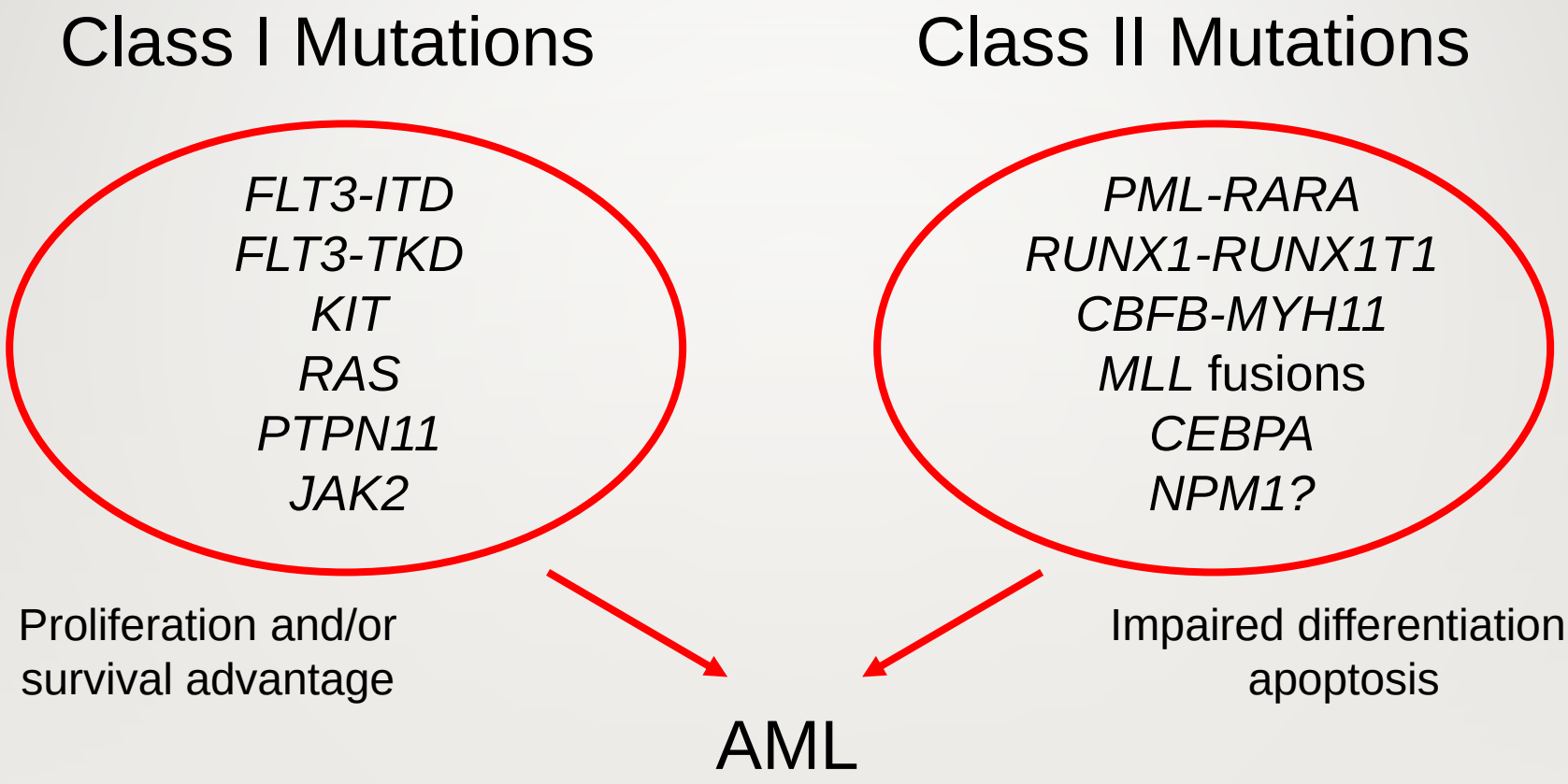
Default offset is +/- 10bps around each exon with exception for *RUNX1*, which has certain intron regions of interest. Also, *NPM1* has coverage set to -30bps before exon 11 because of a downstream polymorphic region.

*Reference transcript numbers may have been updated due to database re-versioning. Refer to the patient report for the most updated gene transcript information.

AML Prognosis based on Genomics

- **GOOD**
  - t(8;21) (M2)
  - t(15;17) (M3)
  - Inv(16) (M4Eo)
- **INTERMEDIATE**
  - Normal karyotype
    - **Good**
      - **NPM1 mut**
      - **CEBPA mut**
    - **Poor**
      - **FLT3-ITD**
      - **High ERG**
      - **High BAALC**
      - **MLL-PTD**
- **POOR**
  - Complex karyotype
    - Complex karyotype
      - 11q23
      - t(6;9) (M2)
      - Inv(3) (M1/5)
      - t(1;22) (M7)
      - MDS
        - 5q-
        - 7q-
        - +8

Two-Hit Hypothesis of Leukemogenesis



Gilliland et al. *Curr Opin Hematol* (2001) 8:189-191. WHO Book 2008

Alphabet Soup of Genes associated with AML

- BAALC gene - Brain and Acute Leukemia cytoplasmic gene
  - Fxn not fully understood
- MLL – Mixed Lineage Leukemia gene
- ERG (Erythroblast transformation specific) Related Gene
  - transcriptional regulator
- FLT3 – Feline McDonough Sarcoma (FMS) Like Tyrosine kinase 3
  - Control cell growth and division
- NPM1
  - Nucleophosmin/nucleoplasmin family of proteins – regulate cell cycle and apoptosis, maintenance of genomic stability, etc.
- RUNX1 – transcription factor involved in hematopoetic cell differentiation

AML General Information

- Most common leukemia in adults
- 15 – 20% of leukemia in children
- Most common in individuals >60
- Lowest survival rate of all leukemias
- Survival rates in younger adults are better than those >60

Case 1

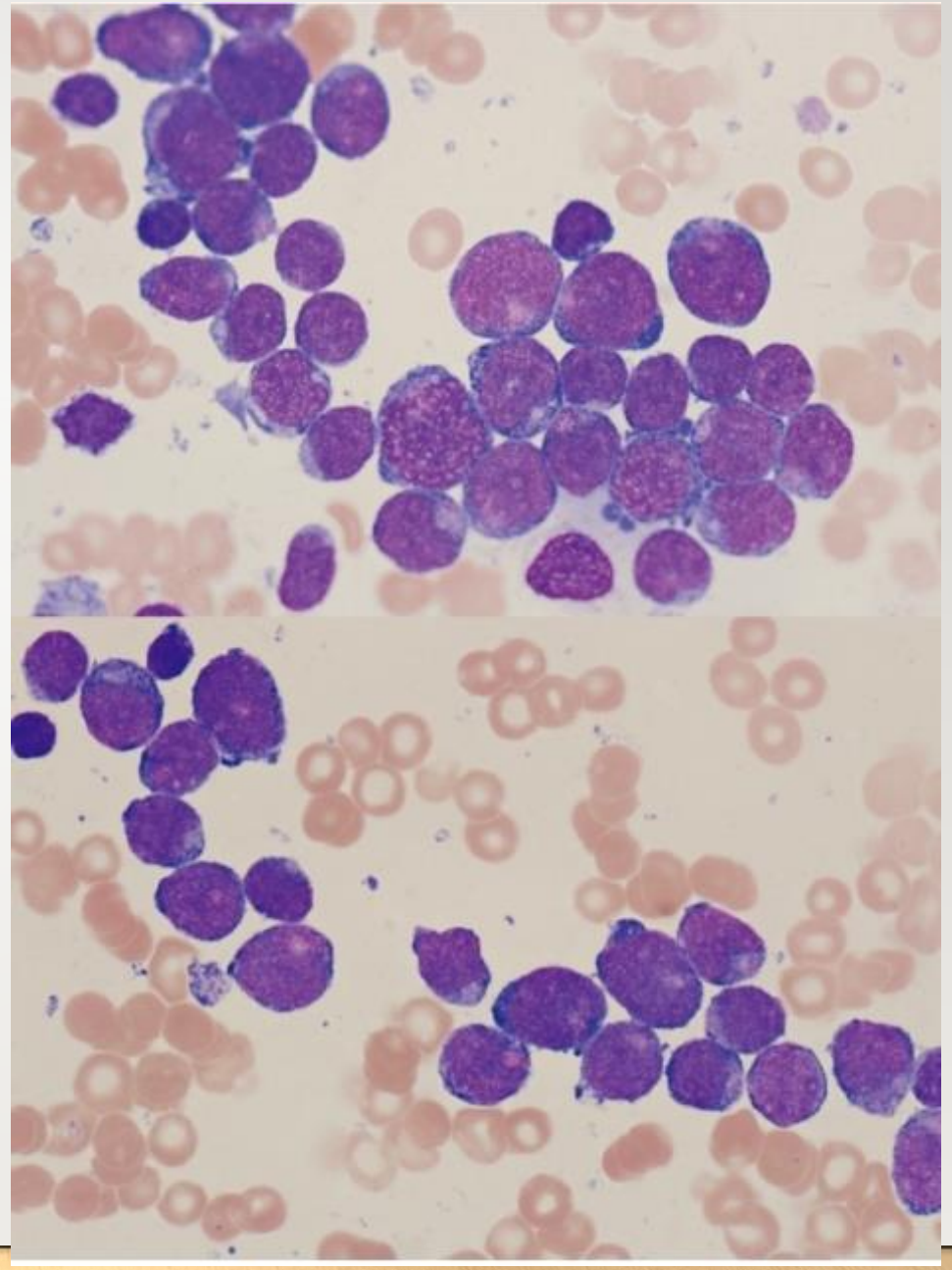
- 3 year old Korean girl
- 5 day history of fever
- Anemic conjunctiva
- No organomegaly

CBC

- Hgb 5.6 g/dL
- WBC 76.5 x 10^3/uL
- Platelet 22 x 10^3/uL
- Diff 86% abnormal myeloid cells

Bone Marrow

- Markedly hypercellular
- 85% blasts
  - Small to medium with coarse nuclear chromatin, distinct nucleoli and basophilic cytoplasm

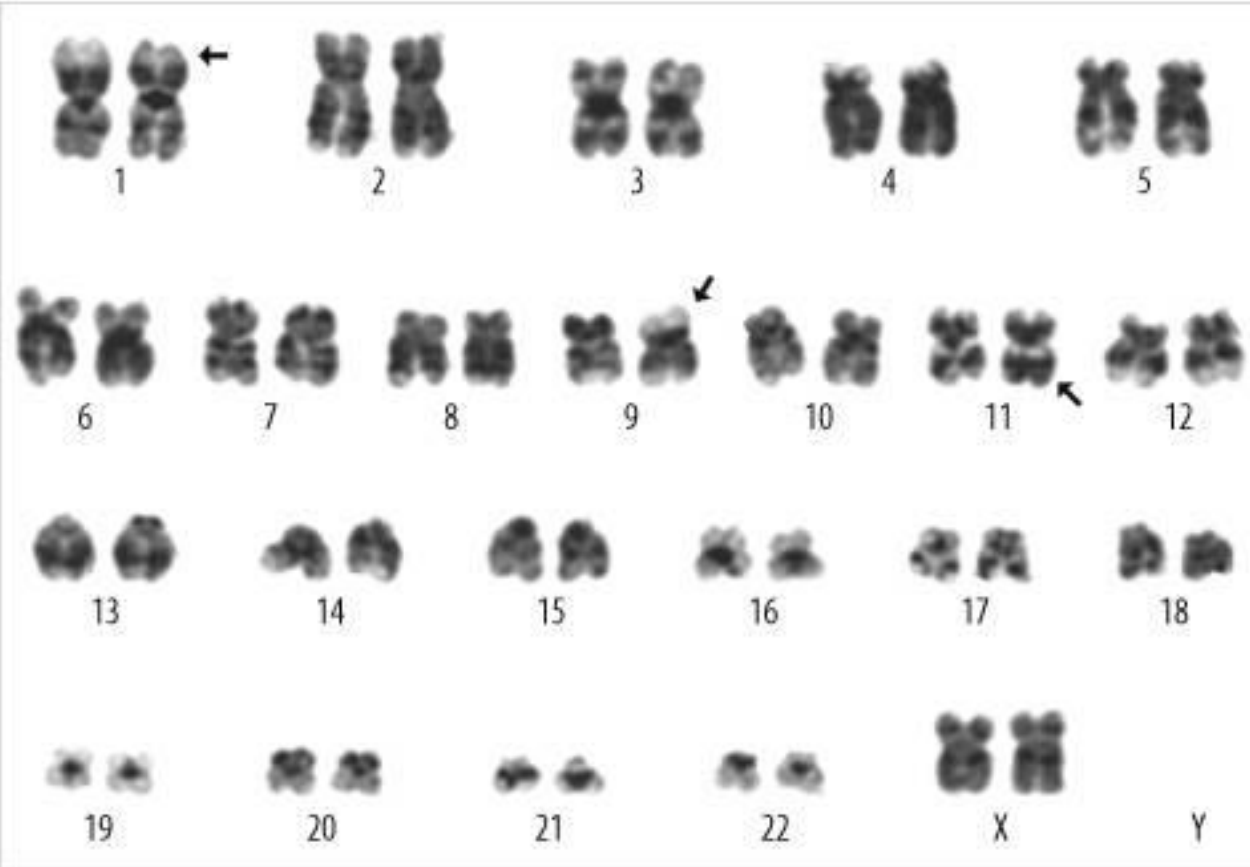


Flow Immunophenotyping/cytochemistry

- Positive for
  - CD13, CD19, CD33, CD34, CD117 and MPO
- Negative for
  - CD2, CD3, CD5, CD7, CD10, CD14, Cd2, CD22, CD56
- Aberrant marker?

Cytogenetic studies

- 46,XX,t(1;9;11)(p34.2;p22;q23) in 19 of 20 cells analyzed



FISH

- MLL/MLLT3 rearrangement confirmed by interphase FISH
- 92% of 200 cells observed at diagnosis

t(9;11)

- Usually associated with monocytic element (FAB M4 and FAB M5)
- 11q23 - Mixed Lineage Leukemia gene (MLL – *now KMT2A*)
- 9p22 –Mixed Lineage Leukemia Translocated to 3 (MLLT3)
- 5 – 6% of AMLs
- Generally poor prognosis but better than other MLL translocations

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APL with t(15;17)*PML-RARA* ***(FAB M3)***

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Provisional entity: AML with BCR-ABL1

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3. Therapy-related myeloid neoplasms

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Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

5. Myeloid sarcoma

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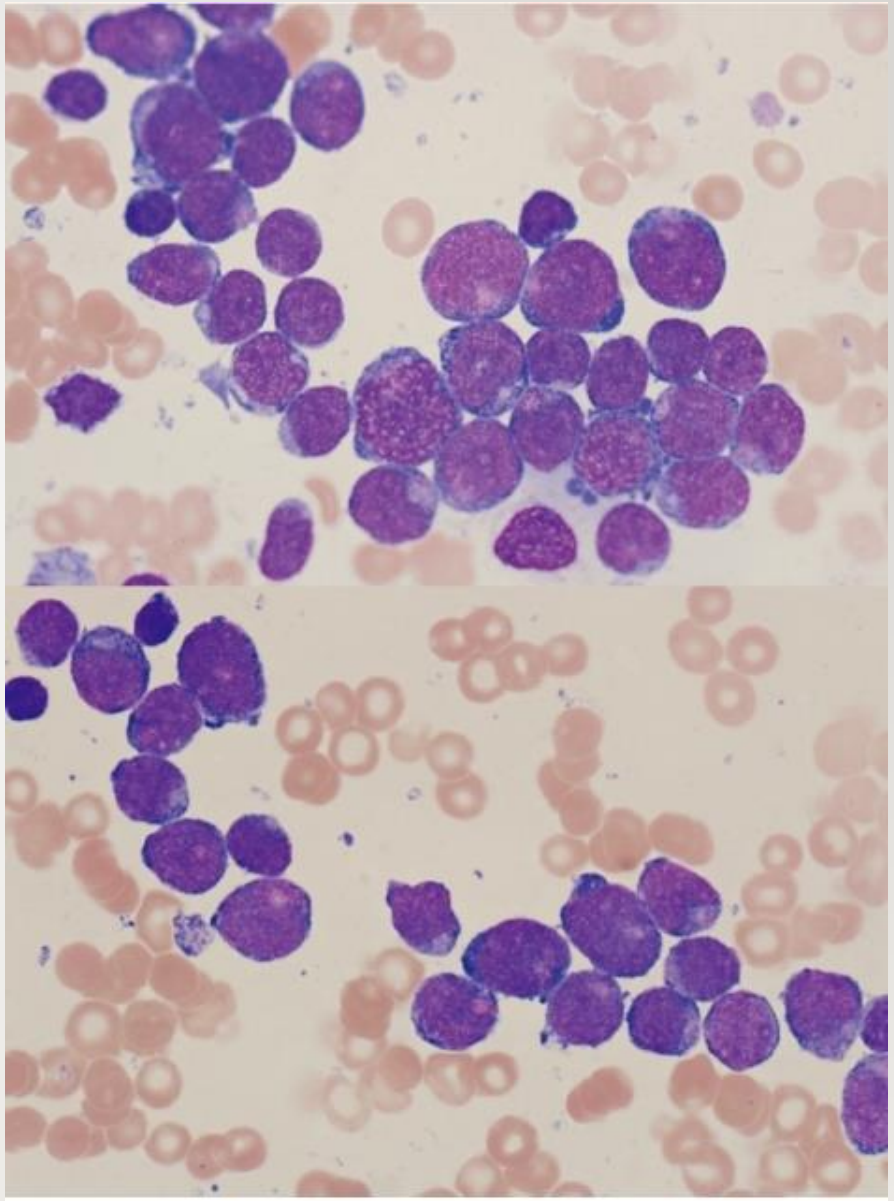
WHO Classification?

- AML with recurrent cytogenetic abnormality
- t(9;11)



Treatment

- Cytarabine, daunorubicin and etoposide followed by consolidation chemotherapy
- At 2 months post treatment
  - MLL rearrangement not present
  - Event free for 6 months after first remission
  - 5 year survival rate is 68% in children <20
  - 26% for >20

Korean J Lab Med 2011; 31(2): 127-129.

Case 2

- 62 year old female
- Generalized weakness, SOB
- Left upper quadrant discomfort
- Bone pain
- Easy bruising
- 20 lb weight loss
- Splenomegaly
- Pulmonary nodules concerning for fungal infection

CBC

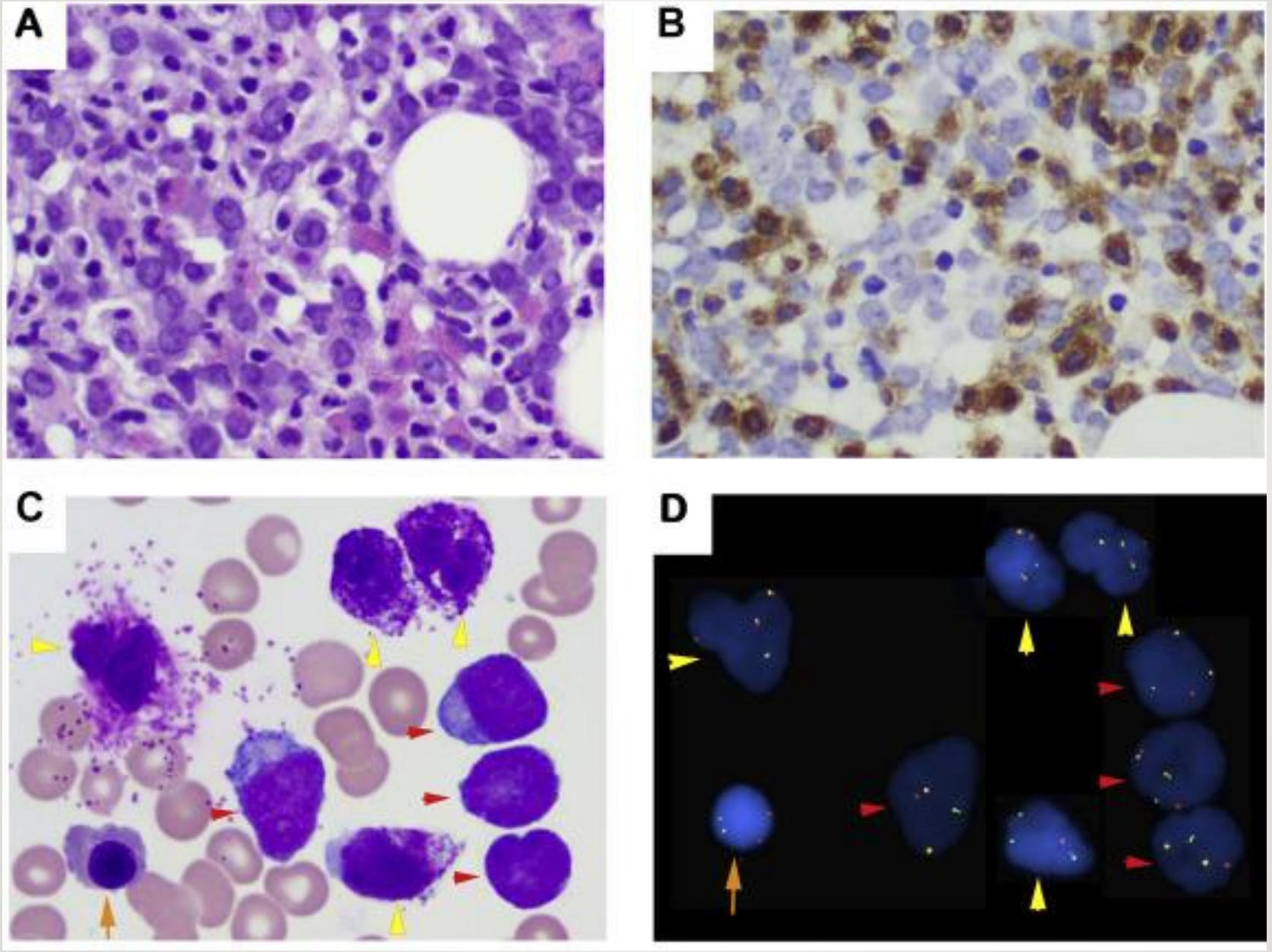
- WBC 4.8 x 10^3/uL
- Hgb 8.2 g/dL
- Platelets 11 x 10^3//uL
- Diff 62% blasts

Bone Marrow Biopsy and Aspiration

- Biopsy – Hypercellular (90%) with markedly increased immature cells admixed with mast cells
- Aspiration – Markedly increased blasts (61%) and mast cells (20%)
  - Blasts were medium to large with distinct nucleoli and rare Auer rods noted
  - Mast cells showed considerable amounts of metachromatic granules, some with degranulation

Bone Marrow Studies

Biopsy with H&E

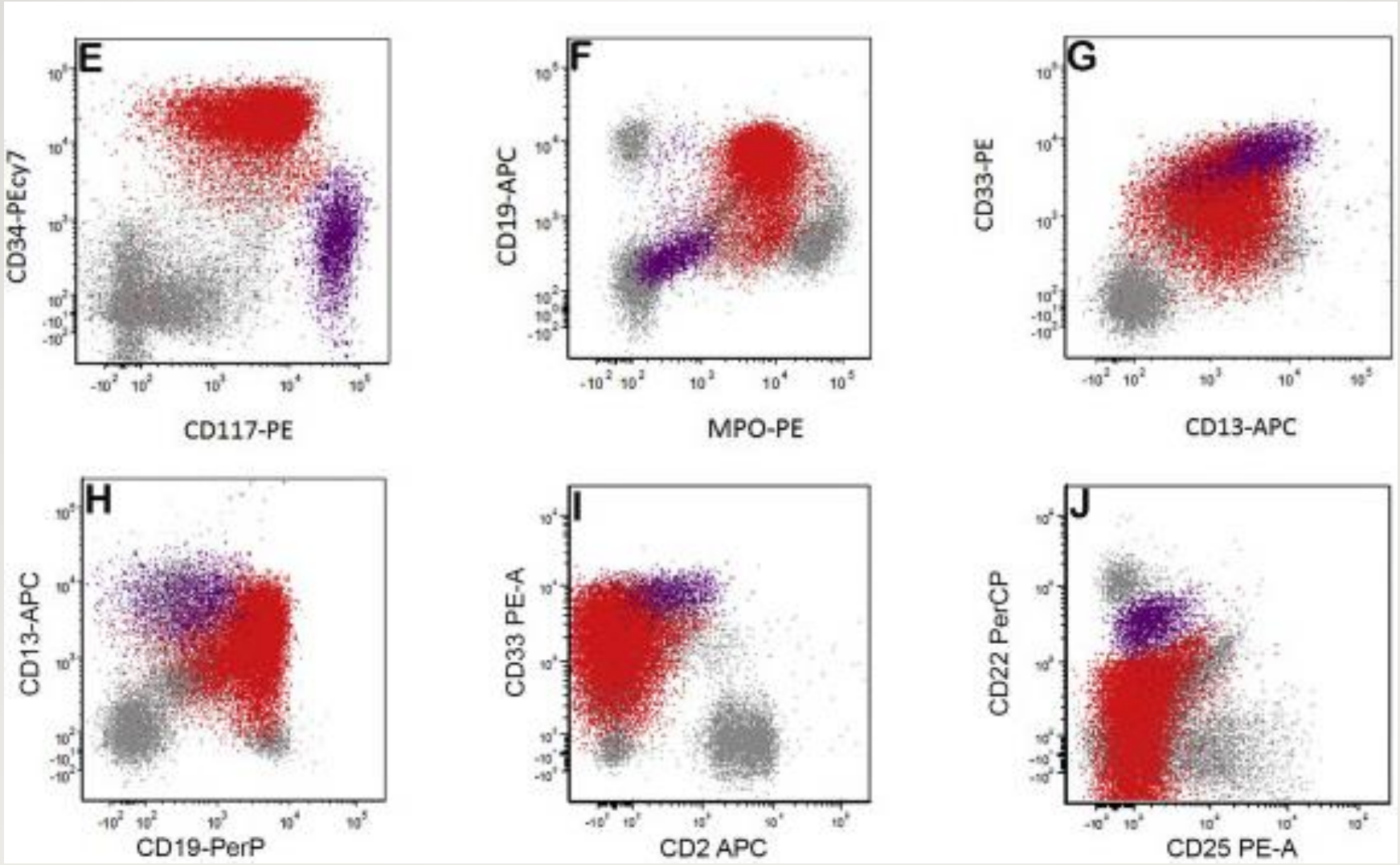


Biopsy with mast cells highlighted with tryptase

Aspiration with Wright/Geimsa

FISH RUNX1/RUNX1T1 fusion

Flow Cytometry Studies

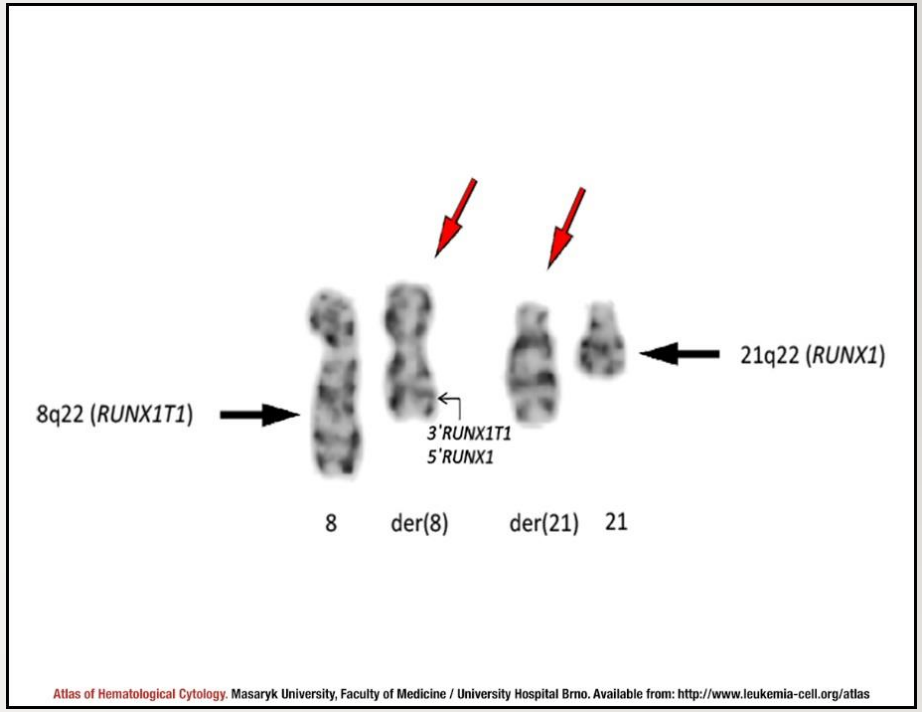


AML with recurrent cytogenetic abnormality

- AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
- *5 – 12% of AML cases*
- Mean age is 30
- Most common AML in children
- FAB M2 – AML with maturation
- Favorable prognosis

t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*

- *RUNX1*
  - Transcription factor essential for differentiation of hematopoietic stem cells
- *RUNX1-RUNX1T1 fusion gene*
  - Transcriptional repressor
  - Causes block in HSC differentiation



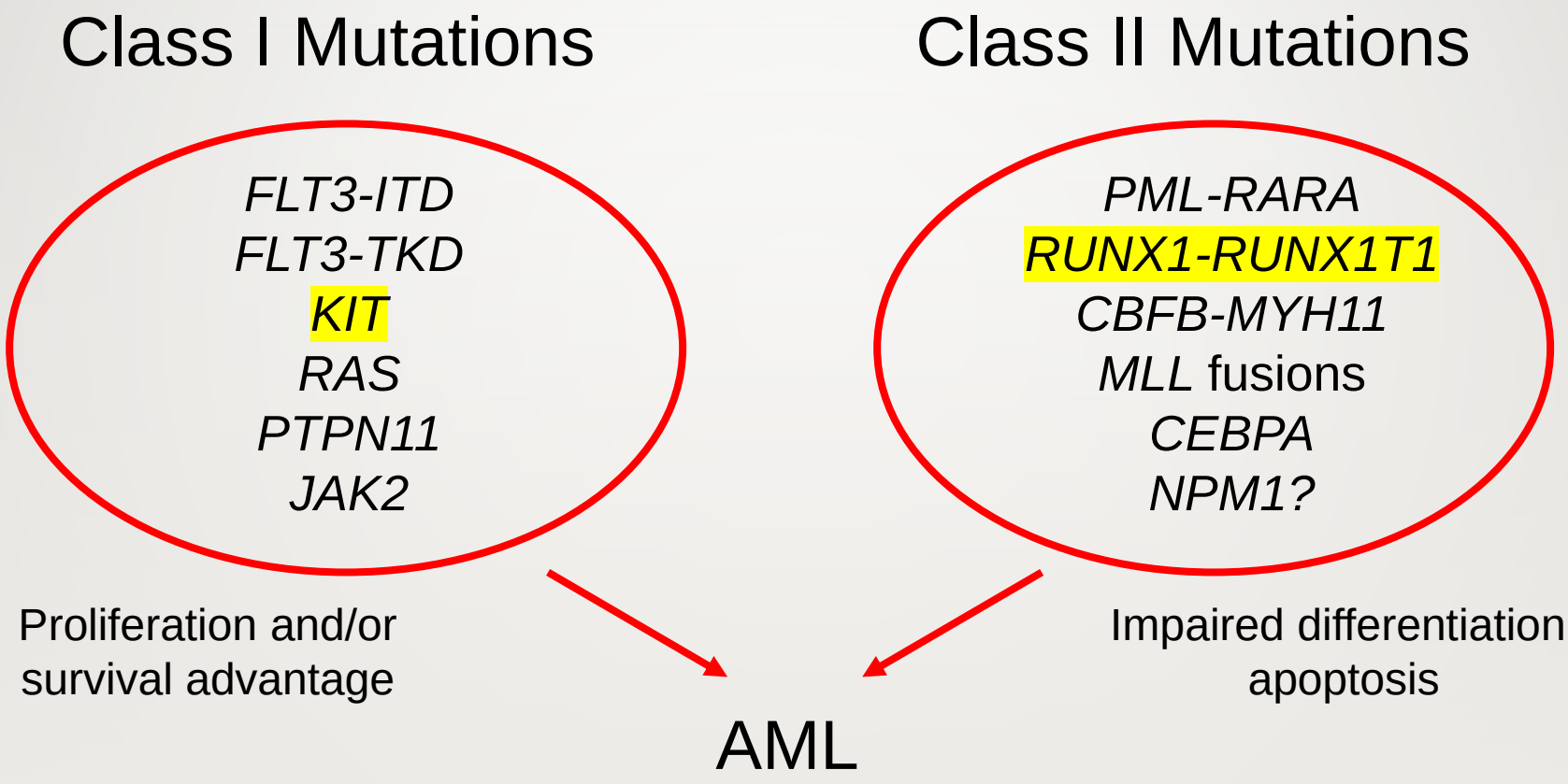
Next Genomic Sequencing

- Used 81 genes frequently mutated in hematopoietic neoplasms
- Detected two mutations in KIT gene

CD117 (c-kit)

- Tyrosine kinase receptor seen in a variety of neoplasms
- Also known as mast/stem cell growth factor receptor
- Regulator of apoptosis, cell differentiation, proliferation
- Mutations are observed in ~20 – 40% of AML with t(8;21) translocation
- Generally poorer prognosis

Two-Hit Hypothesis of Leukemogenesis



Gilliland et al. *Curr Opin Hematol* (2001) 8:189-191. WHO Book 2008

Treatment

- Fludarabine – DNA inhibitor
- Cytarabin – inhibits DNA synthesis
- Idarubicin – DNA antagonist
- Gemtuzumab (anti CD33 antibody – 1991; approved for AML)
- G-CSF

Outcome

- Patient failed to achieve remission
- Had complications including respiratory distress
- Died of multiorgan failure 50 days/= post diagnosis
- Patients with concurrent Systemic Mastocytosis and AML t(8;21) often have poor outcomes

Case 3

- 57 year old female
- Admitted to ER with weakness, fatigue and multiple bruises
- Flu – like symptoms
- PE
  - Pallor, petechiae on arms and trunk

www.ncbi.nlm.nih.gov/pmc/articles/PMC7154239/

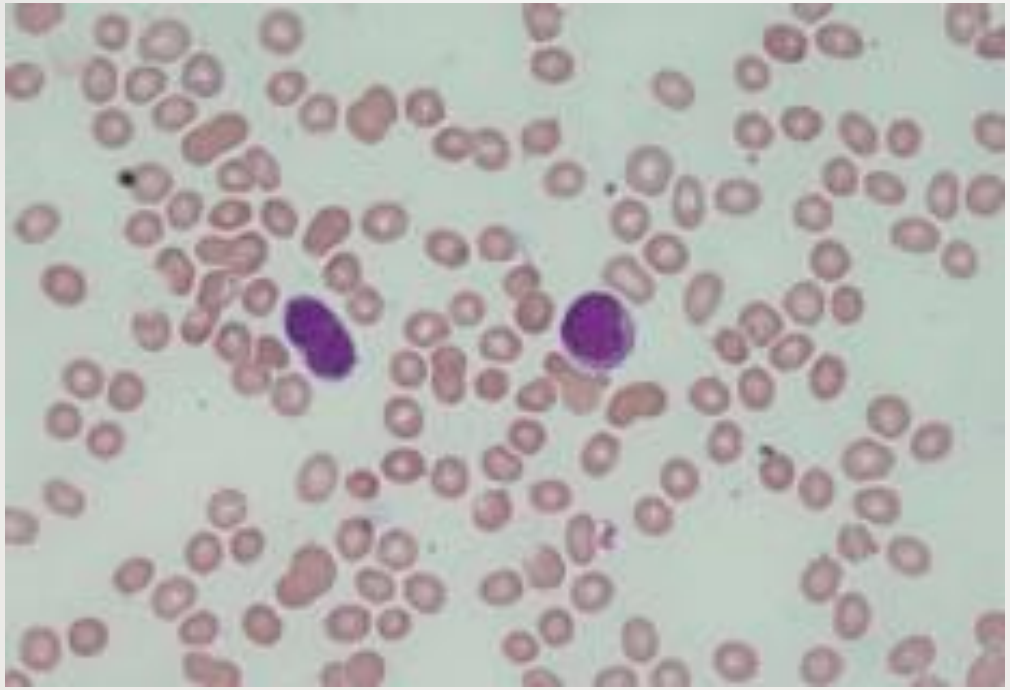
Physical exam

- Petechiae on lower extremities, upper torso and upper extremities
- Purpuric lesion on tip of tongue
- No hepatosplenomegaly or lymphadenopathy
- Bone marrow and other blood tests ordered

Lab results

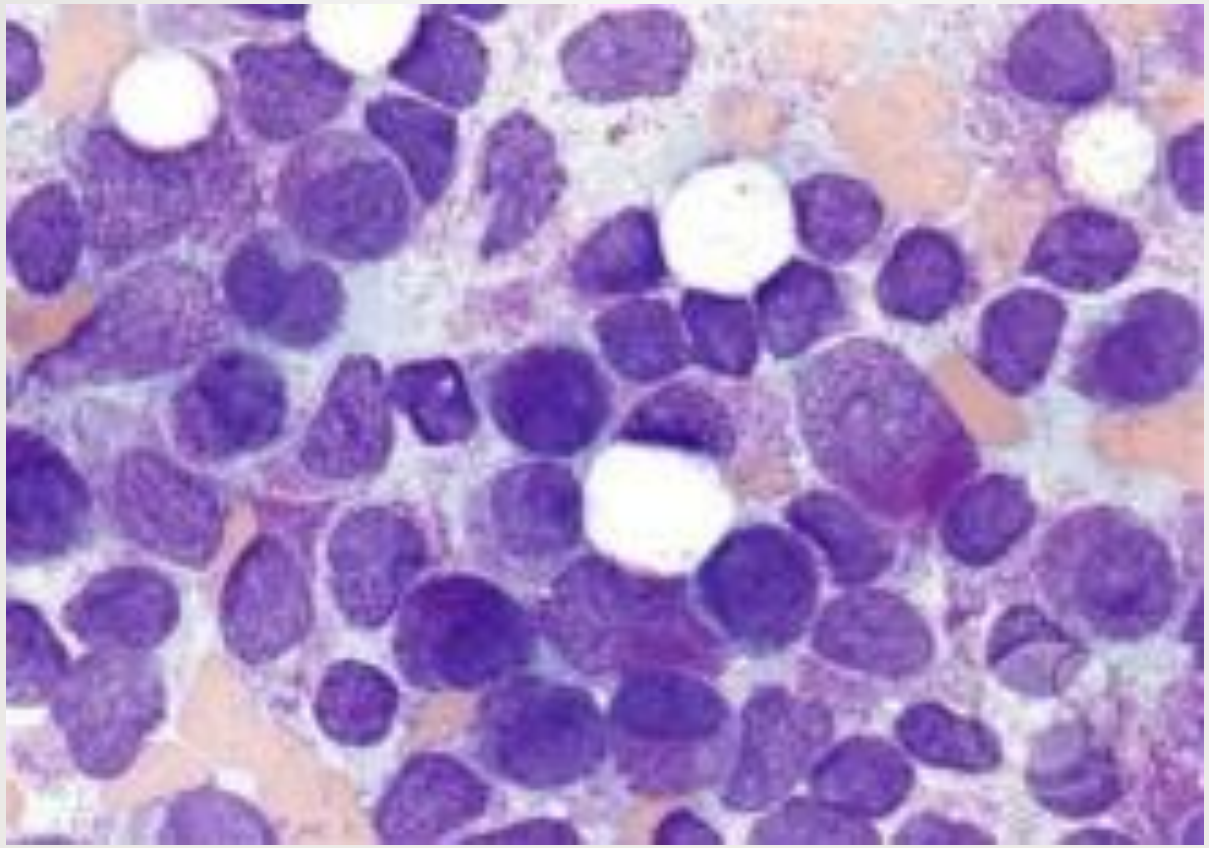
Test	Patient Results	Normal Range	
Hgb	8.3g/dL	13.5 – 16.0	
Hct	23.6%	37.0 – 47.0	
RBC	2.5 x 10^6/uL	4.2 - 5.4	
Platelets	21 x 10^3/uL	150 – 400	
WBC	11.9 x 10^3/uL	4.8 – 10.8	
PT	33 sec	9 - 13	
APTT	41 sec	24 - 37	

Blood Smear



Predominance of promyelocytes with bilobed nuclei with hypogranulation

Bone Marrow

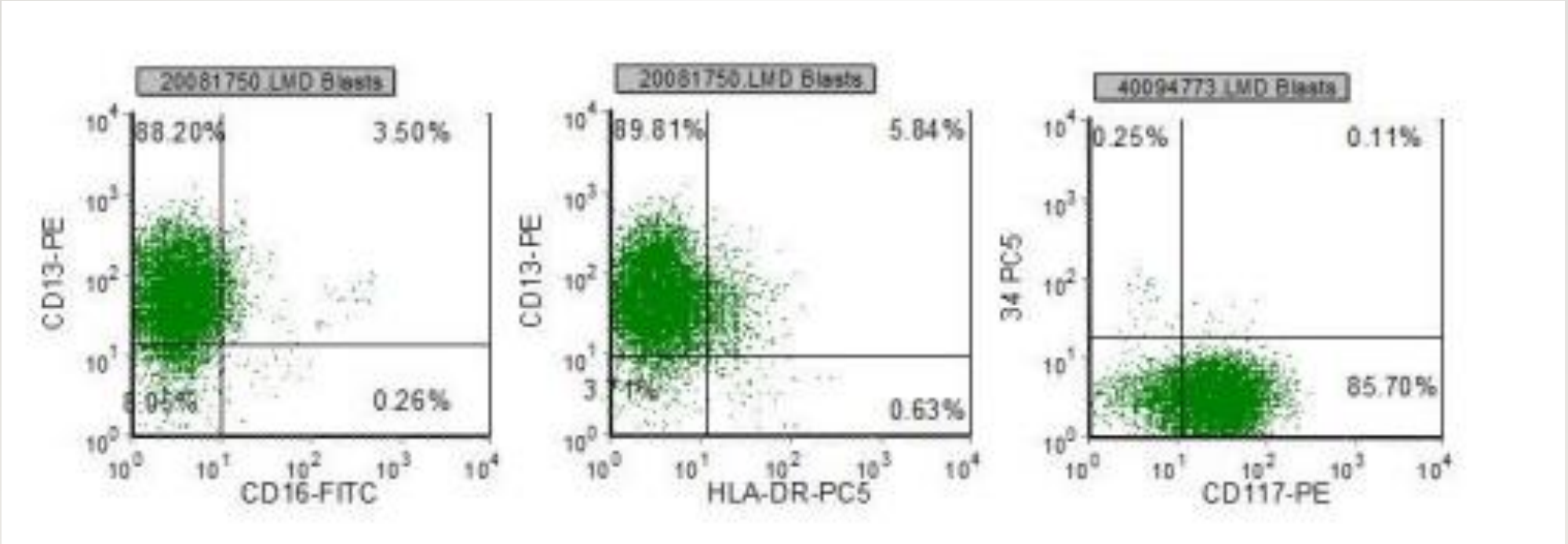


83% Immature cells

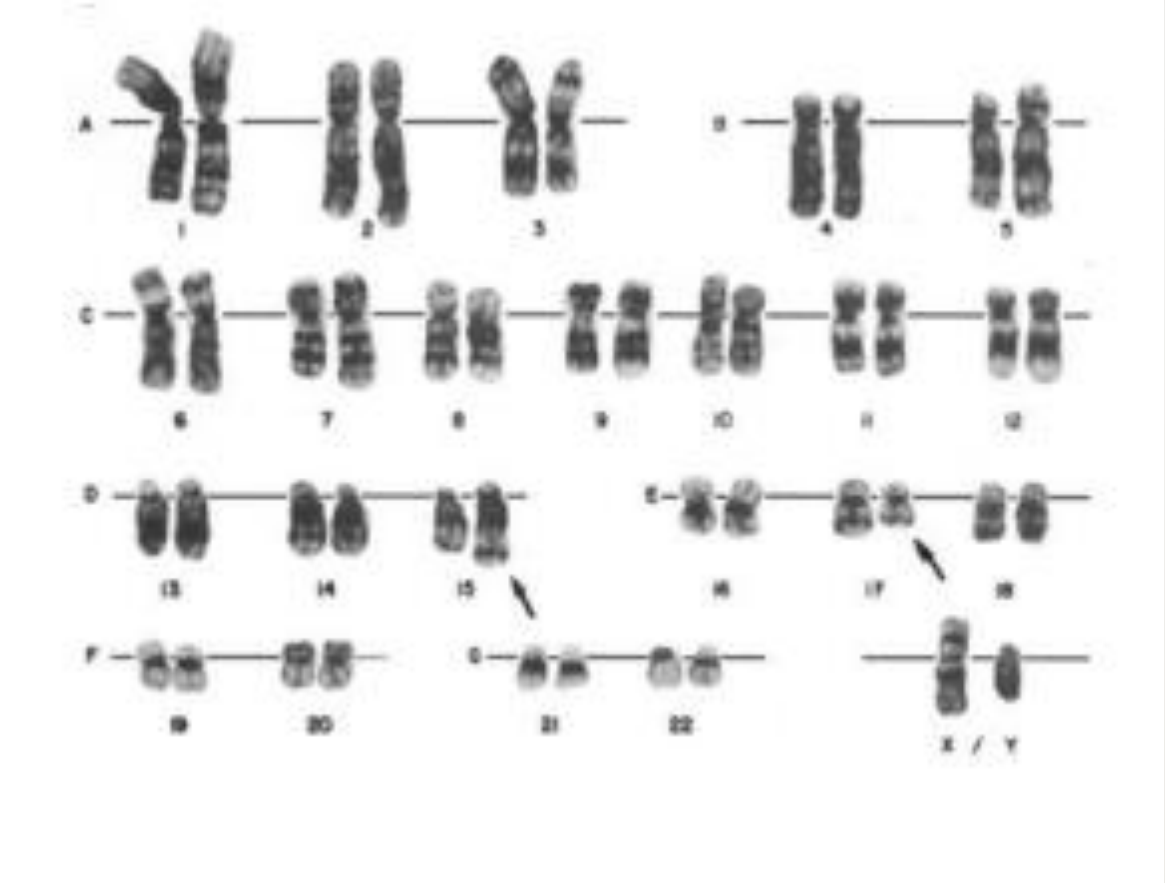
Cytochemistry

- MPO and SBB – strong reaction to both
- Myeloid lineage

Flow Cytometry

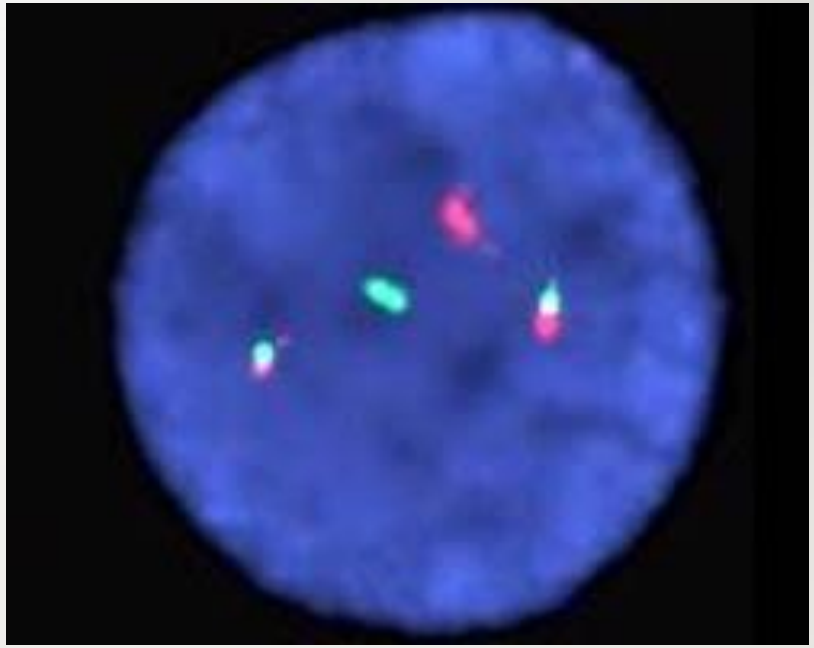


Cytogenetics – t(15;17)



FISH

- Normal chromosomes 15 and 17
  - Green and Red
- Two fusion chromosomes
  - der(15) and der(17)

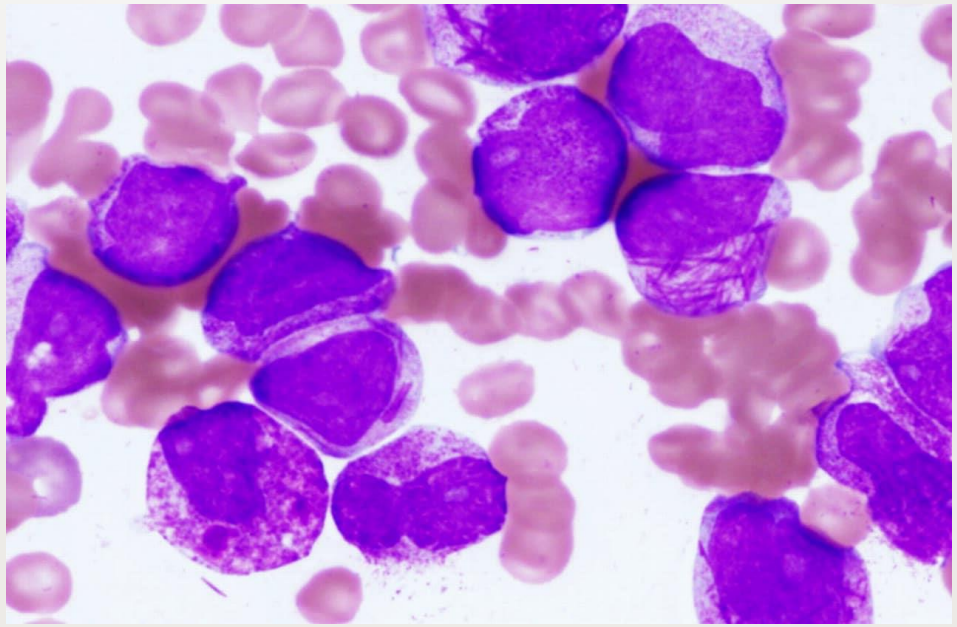


Diagnosis? **AML with Recurrent Genetic Abnormalities**

- APL with t(15;17)*PML-RARA* ***(FAB M3)*** **-** Acute Promyelocytic Leukemia
- 5 – 10% of AML cases
- Occurs in all age groups
- Seen most commonly in young adults
- Associated with high risk of DIC

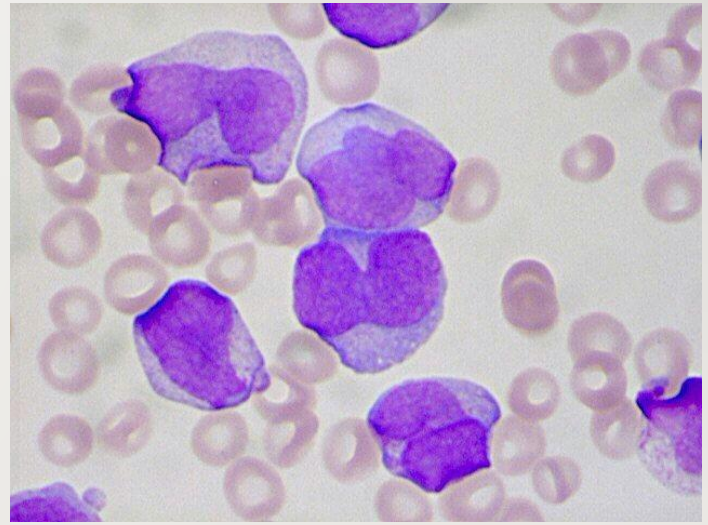
Two variants of APL

- Both variants associated with high risk of DIC
- Typical variant
  - Abnormal hypergranular promyelocytes with Auer rods



Two variants of APL

- Microgranular variant
  - Granules cannot be visualized with light microscope
  - 15 - 40% of APL cases
  - Nucleus appears “butterfly shaped” or bilobed



APL and RARα Genes

- APL gene
  - growth suppressor and proapoptotic activity
- RARα gene
  - Transcription factor called retinoic acid receptor, alpha
  - Important for promyelocyte maturation
- Fusion gene - PML/RARα
  - Produces abnormal protein that blocks differentiation and allows for abnormal proliferation of promyelocytes

Treatment

- ATRA – All Trans Retinoic Acid
- Early – late 80’s and early 90’s
- Targeted therapy
  - Classified as a retinoid
    - Relative of Vitamin A
    - Retinoids control cell growth, differentiation and cell death
- Caused promyelocytes to mature and undergo spontaneous apoptosis
- Revolutionized treatment and survival rates
- Short lived remission without addition of Arsenic Trioxide
  - Induces apoptosis and differentiation
- 2 year event free survival rate is 99%
- Maintenance therapy generally not needed in patients who achieve CR with ATRA and ATO

Back to our patient

- Patient treated with ATRA and ATO along with anthracycline
  - Most recent studies suggest that ATRA and ATO alone works best in most cases
- Patient experienced complete remission and continued to be cancer free

AML Research and Treatment

- Many different types of AML
- Gene mutations affect disease progression and response to treatment
- Chemotherapy still main treatment for most types of AML
  - Sapacitabine
  - Laromustine
  - Guadecitabine
- Ongoing research and clinical trials in developing and testing newer targeted therapies

Targeted therapy drugs

- FLT3 inhibitors
  - Midostaurin and Gilteritinib
- IDH (Isocitrate Dehydrase) Inhibitors
  - Enasidenib
  - Ivosidenib

Immunotherapy

- Monoclonal antibodies
  - Gemtuzumab ozogamicin – Antibody to CD33 with poison attached to it
- CAR T-cell therapy
  - Patient's T-cells are altered to give them Chimeric Antigen Receptors to help them attach to leukemic cells
  - Altered T cells are grown in lab and infused back into patient
  - Attack leukemic cells
  - Very expensive and some serious side affects
    - $375,000 for a one-time treatment
    - Medicare will cover for certain cancers
      - ALL and non-Hodgkin lymphoma
      - More than 20 clinical trials for patients with AML

Summary

- **W**orld **H**ealth **O**rganization Classification of **A**cute **M**yeloid **L**eukemia
- Laboratory testing essential to the diagnosis and treatment of AML
- Discussed case studies of several different types of AML
- Reviewed some targeted therapies for AML

References

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