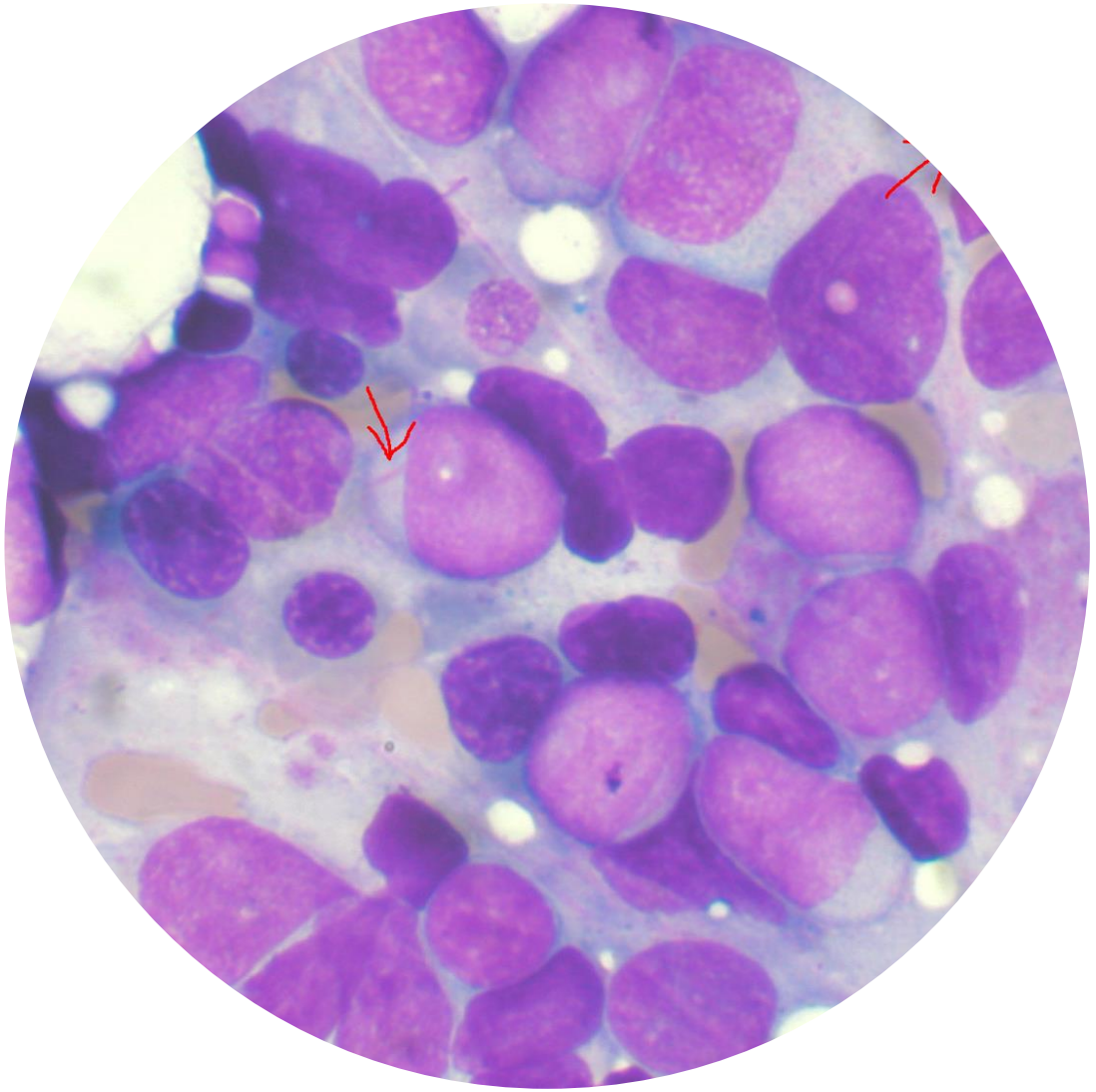


Malignant Myeloid Disorders

Pinal Patel, MLS (ASCP)^{CM}

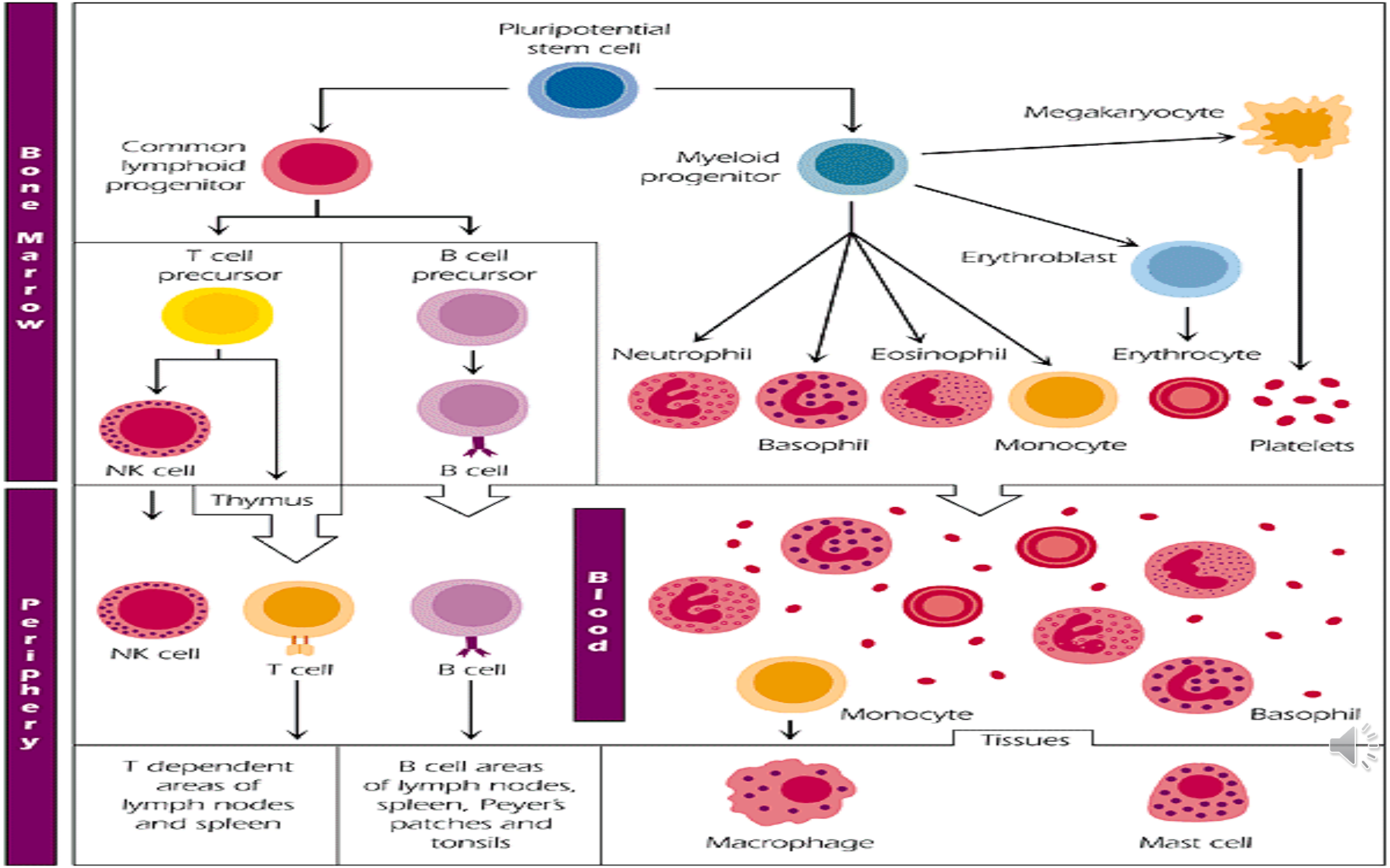
Definitions

Leukemia

- Originate in the bone marrow and readily pass into peripheral blood
- Ability to infiltrate lymphoid tissues and other organs

Lymphoma

- Solid tumors of lymphoid cells
- Originate in lymphatic systems
- Proliferate in lymph nodes, lymphoid organs and tissues and can circulate in peripheral blood.


Bone Marrow
Periphery
Pluripotential stem cell
Common lymphoid progenitor
Myeloid progenitor
Megakaryocyte
T cell precursor
B cell precursor
Erythroblast
Neutrophil
Eosinophil
Erythrocyte
NK cell
B cell
Basophil
Monocyte
Platelets
Thymus
NK cell
T cell
B cell
Blood
Monocyte
Basophil
Tissues
T dependent areas of lymph nodes and spleen
B cell areas of lymph nodes, spleen, Peyer's patches and tonsils
Macrophage
Mast cell

Hematography® Plus

Blood Cell Maturation

K. Lofsness
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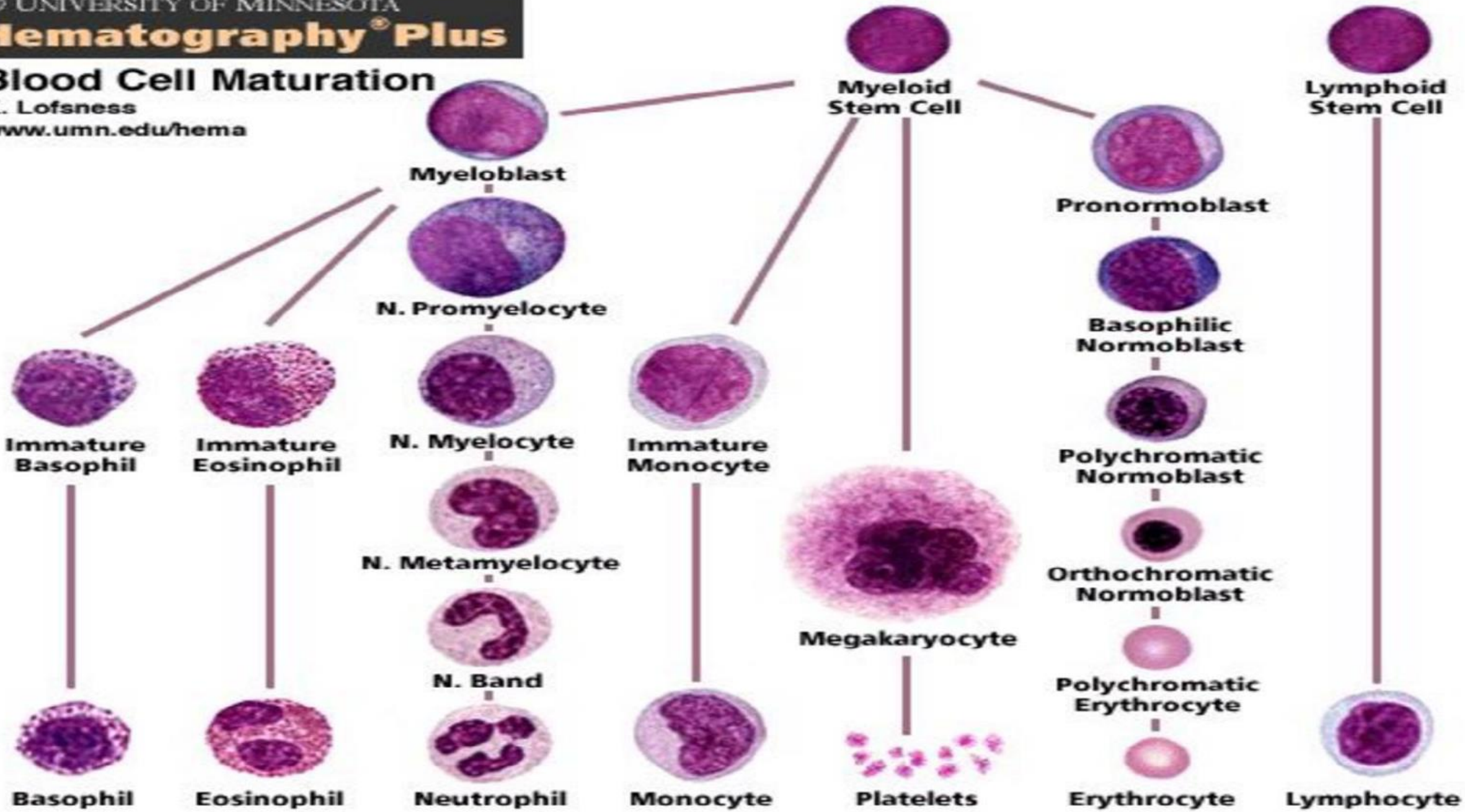


How do we determine cell of origin?

- Morphology on Wright/Giemsa stain of smears (bone marrow, PB) or H&E stained tissue sections
- Cytochemical stains detect various enzymes within a cell by looking for products of their reactions, eg. Myeloperoxidase, TRAP
- Immunophenotyping using antibodies against molecules found on the cell surface
- Flow cytometry (cells in suspension)
- Immunohistochemistry (tissue sections)

Etiology of Hematologic Neoplasms

Genetic factors

Down syndrome- ALL or AML

Fanconi anemia- AML

Ataxia Teleangiectesia- ALL,NHL

Acquired disorders

PNH and aplastic anemia may transform into AML

Environment factors

Ionizing radiation, alkylating agents , chemotherapy drugs

Viruses

HTLV-1, EBV

Etiology and Pathogenesis

- Etiology: Unknown
- Numerous risk factors may cause mutations in the gene involved in regulating cell proliferation and differentiation
  - Oncogenes and tumor suppressor genes

Proto-oncogenes and Oncogenes

- Proto-oncogene: normal gene coding a protein that helps cells grow and has the potential to become an oncogene
- Oncogene: altered gene that cause dysregulated growth
- Located at breakpoints of chromosomal aberrations (translocations)
- Gain-of-function

Tumor suppressor genes

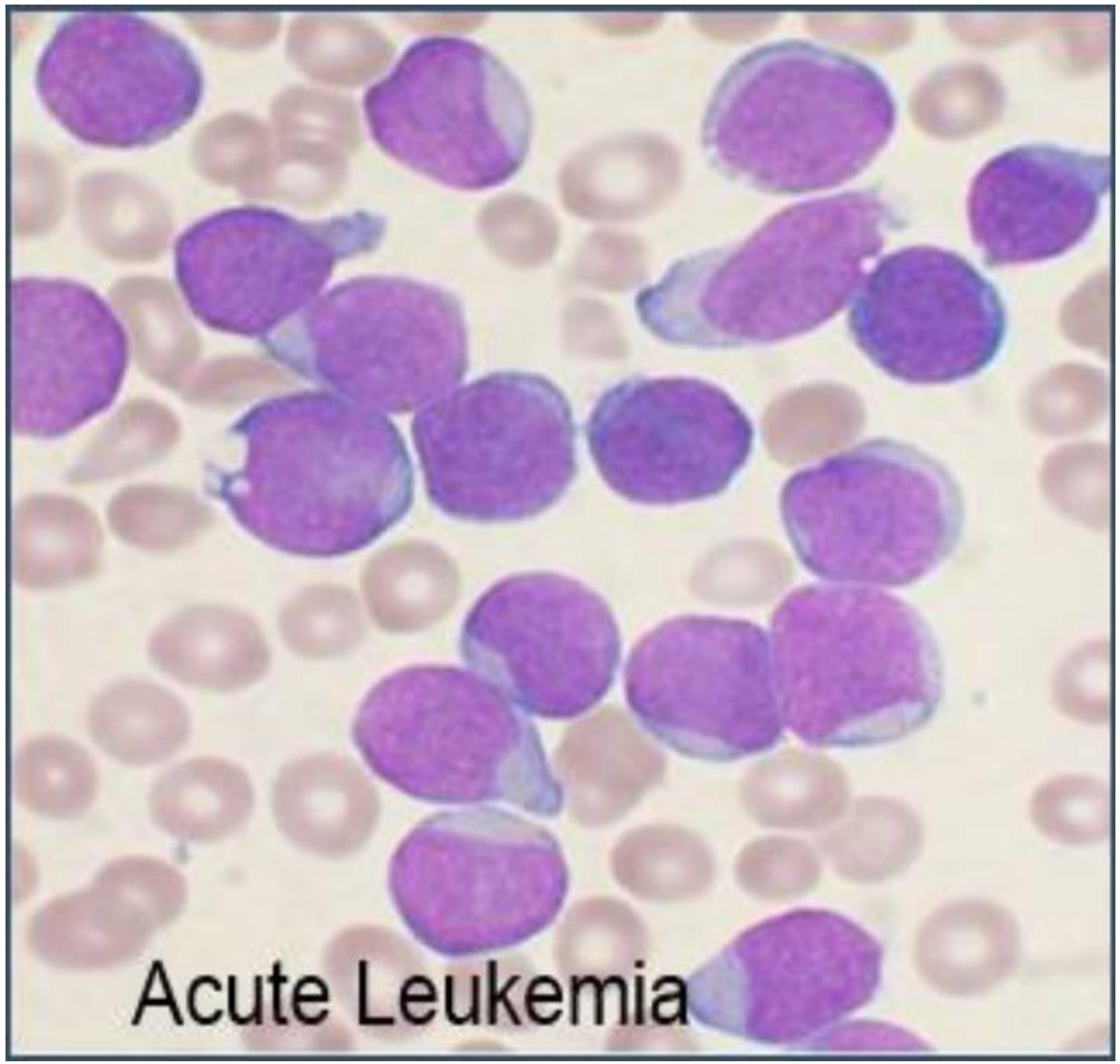
- Encode proteins which help to slow growth or destroy any cell that is not reproducing or functioning properly (apoptosis)
- Loss-of-function
- Often requires a “double hit” to cause cancer because then both alleles are lost
- Someone who inherited one “hit” is at higher risk for cancer at baseline

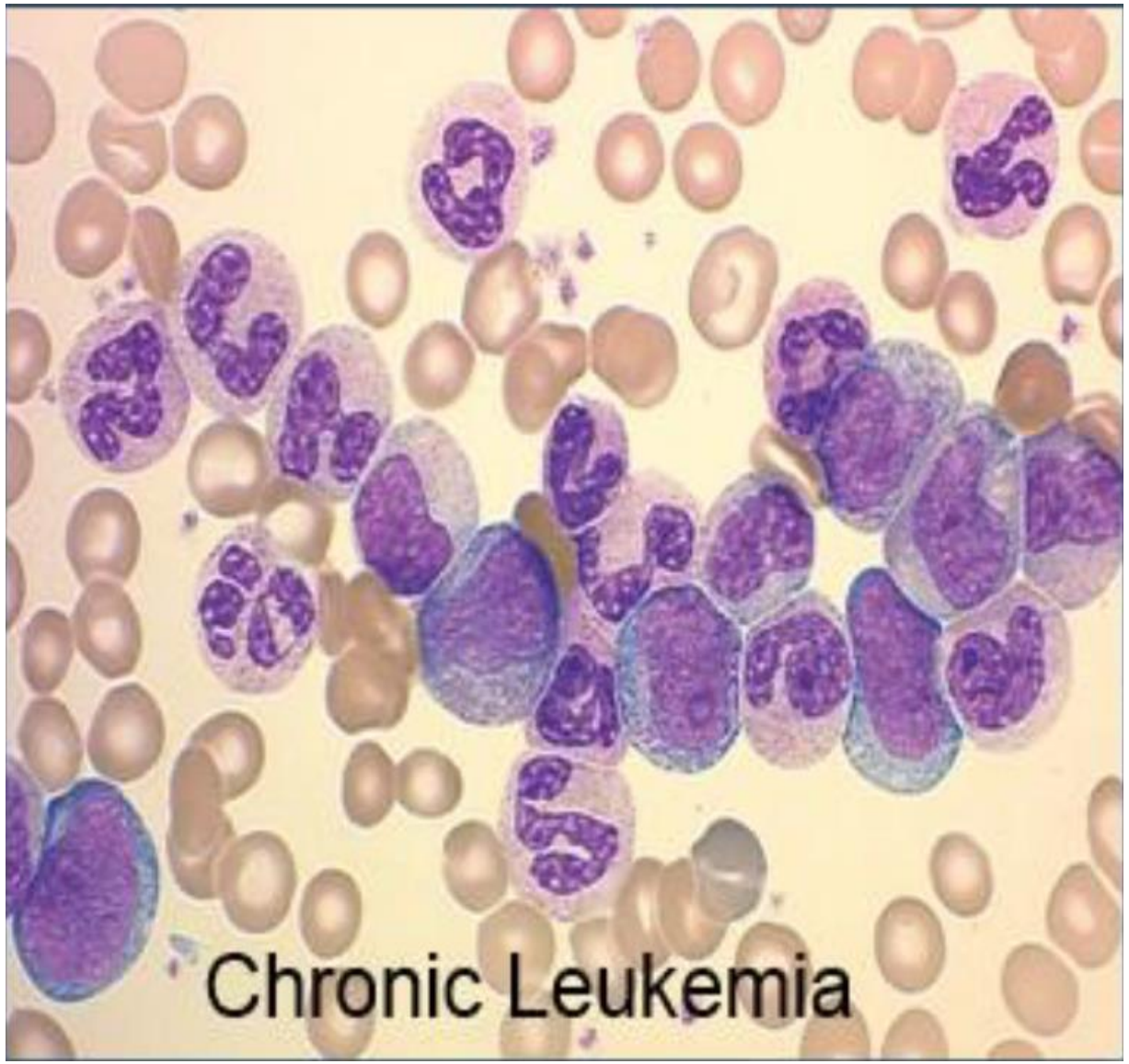
Myeloid Neoplasms

- Acute Myeloid Leukemia (AML)
- Myeloproliferative neoplasms (MPN)
- Myelodysplastic syndromes (MDS)
- Myelodysplastic/myeloproliferative neoplasms

Other classes of myeloid neoplasms

- Mastocytosis
- Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement
- Myeloid neoplasms with germline predisposition


Acute Leukemia


Chronic Leukemia

How do these diseases affect the patient?

- The malignant cells don’t function properly and inhibit the production/function of normal blood cells
  -Anemia, bleeding, infection
- Things which start out slowly (chronic) and are associated with mild abnormalities can “transform” into acute lesions with higher mortality
- Malignant cells also have some bad properties can cause vascular occlusion, etc.

Classifications

- Standard was WHO rev 4th ed(2016)
- Recently two new classifications
  - -International Consensus Classification
  - -WHO 5th ed(in beta)
- Trend toward increased use of molecular (eg. TP53 mutations)/cytogenetic data to define diseases

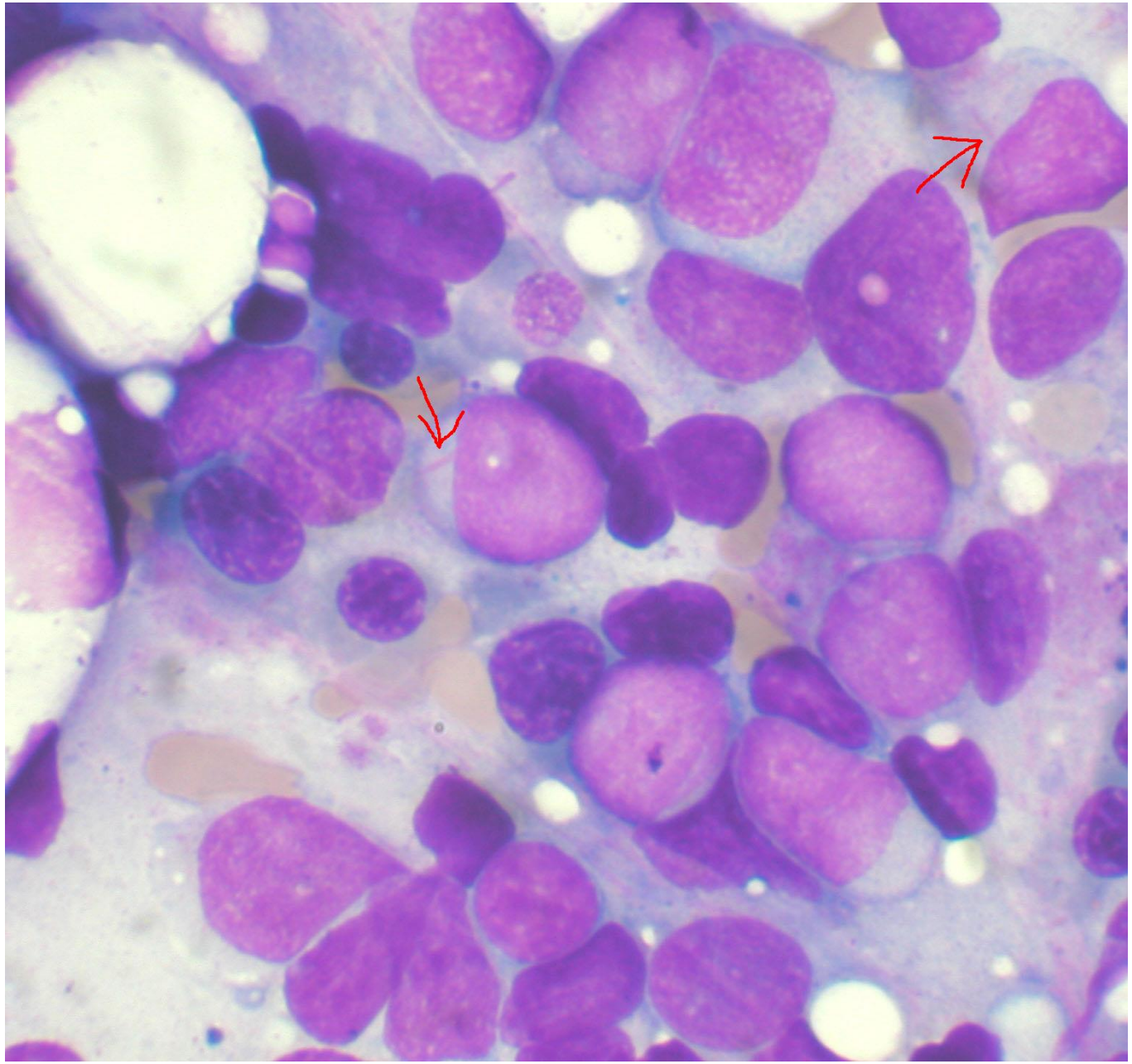
Acute Myeloid Leukemia(AML)

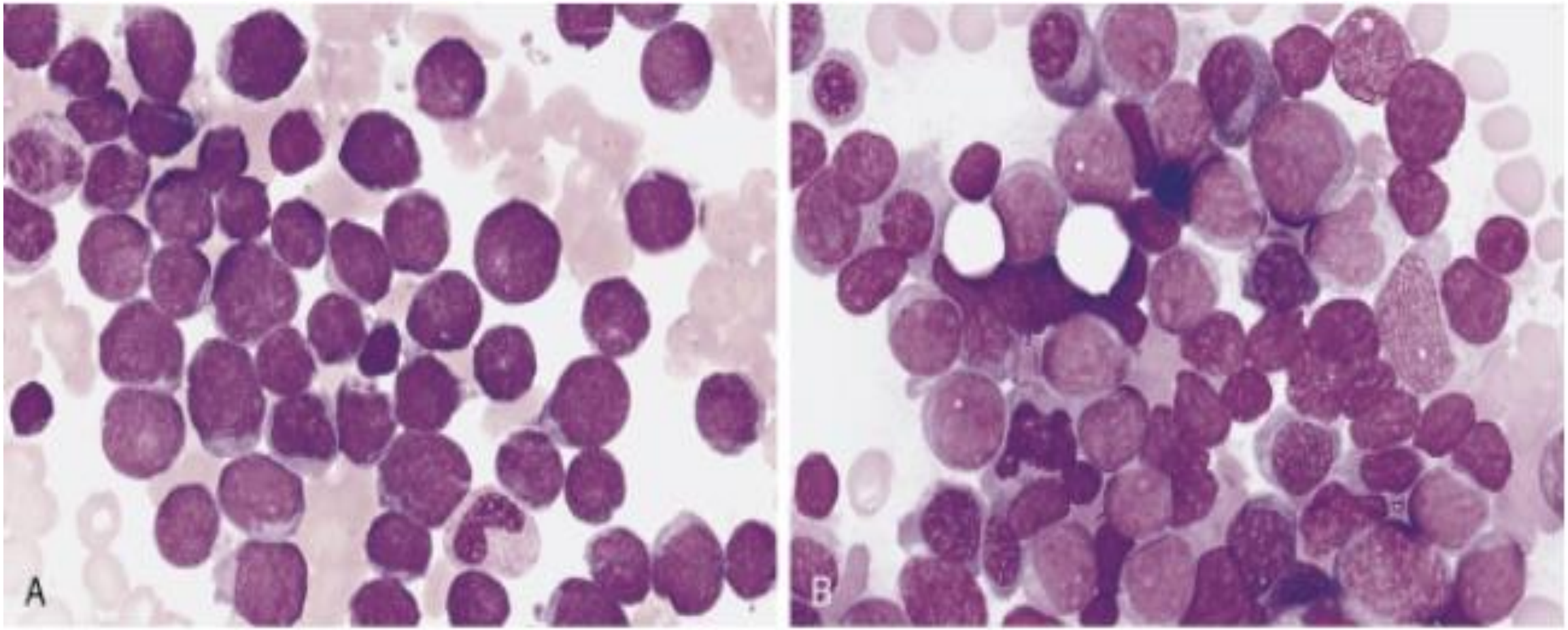
- Malignant, clonal disease that involves proliferation of myeloid blasts in bone marrow, peripheral blood or other tissue.
- Most common acute leukemia in adults (80%)
    - -15-20% of acute leukemia in children
- Decreased production of normal bone marrow elements
- ≥20% blasts in bone marrow OR peripheral blood
    - -Or leukemia defining translocations/mutations

Acute Myeloid Leukemia(AML)

- Laboratory findings:
  - WBC is low, decreased or increased
  - Low hemoglobin
  - Low platelets
  - Hyperuricemia, hyperphosphatemia and hypocalcemia
- PB smear with myeloblasts
- The presence of auer rods
  - crystallization of primary granules so myeloperoxidase, Sudan black B positive
  - pathognomonic of acute myeloid leukemia, and any neoplasm with increased myeloid blasts

Auer Rods




A
B

FAB Classification (1976)

categorized by cell line as defined by cytochemistry and maturity

- M0: Minimally differentiated–barely myeloid
- M1: AML without maturation –<10% promyelocytes or further maturation. (positive for MPO or Sudan Black B)
- M2: AML with maturation –>10% cells beyond promyelocyte maturation
- M3: Acute promyelocytic leukemia –promyelocytes
- M4: Myelomonocytic–myeloid blasts and monoblasts /promonocytes
- M5: Monoblastic-≥ 25% monoblasts, promonocytes or monocytes (alpha-naphthyl butyrate esterase positive)
- M6: Erythroleukemia -erythroblasts or myeloid blasts + erythroblasts (PAS+)
- M7: Megakaryoblastic -≥ 30% of blasts are of megakaryocytic lineage

WHO 2017 Classification AML

- Acute myeloid leukemia with recurrent genetic abnormalities
  - -Translocations and mutations
- Acute myeloid leukemia with myelodysplasia related changes
- Therapy related myeloid neoplasms
- Acute myeloid leukemia, not otherwise specified
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

Table 26. Classification of acute myeloid leukemia (AML) with percentage of blasts required for diagnosis

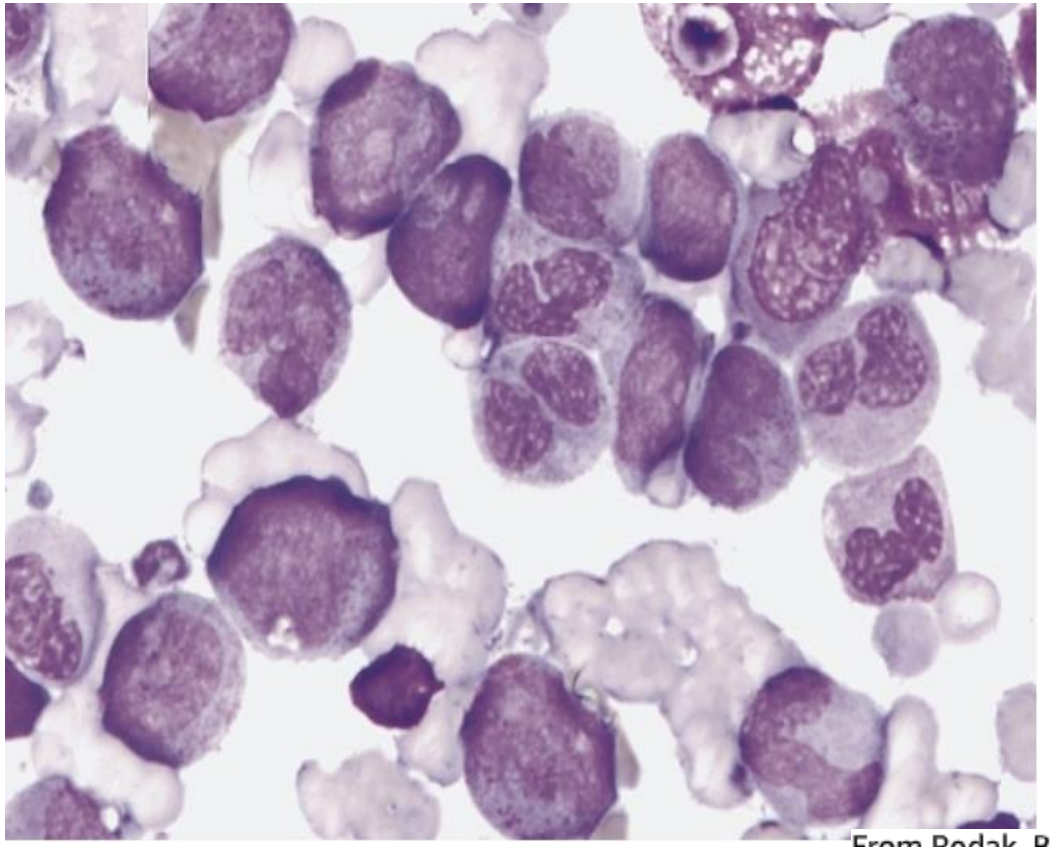
- Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA* ≥10%
- APL with other *RARA* rearrangements* ≥10%
- AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ≥10%
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ≥10%
- AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ≥10%
- AML with other *KMT2A* rearrangements** ≥10%
- AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214* ≥10%
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*) ≥10%
- AML with other *MECOM* rearrangements*** ≥10%
- AML with other rare recurring translocations (see Supplemental Table 5) ≥10%
- AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*‡ ≥20%
- AML with mutated *NPM1* ≥10%
- AML with in-frame bZIP *CEBPA* mutations ≥10%
- AML and MDS/AML with mutated *TP53*† 10-19% (MDS/AML) and ≥20% (AML)
- AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥20% (AML)
  - Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥20% (AML)
  - Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
- AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥20% (AML)
- Myeloid Sarcoma

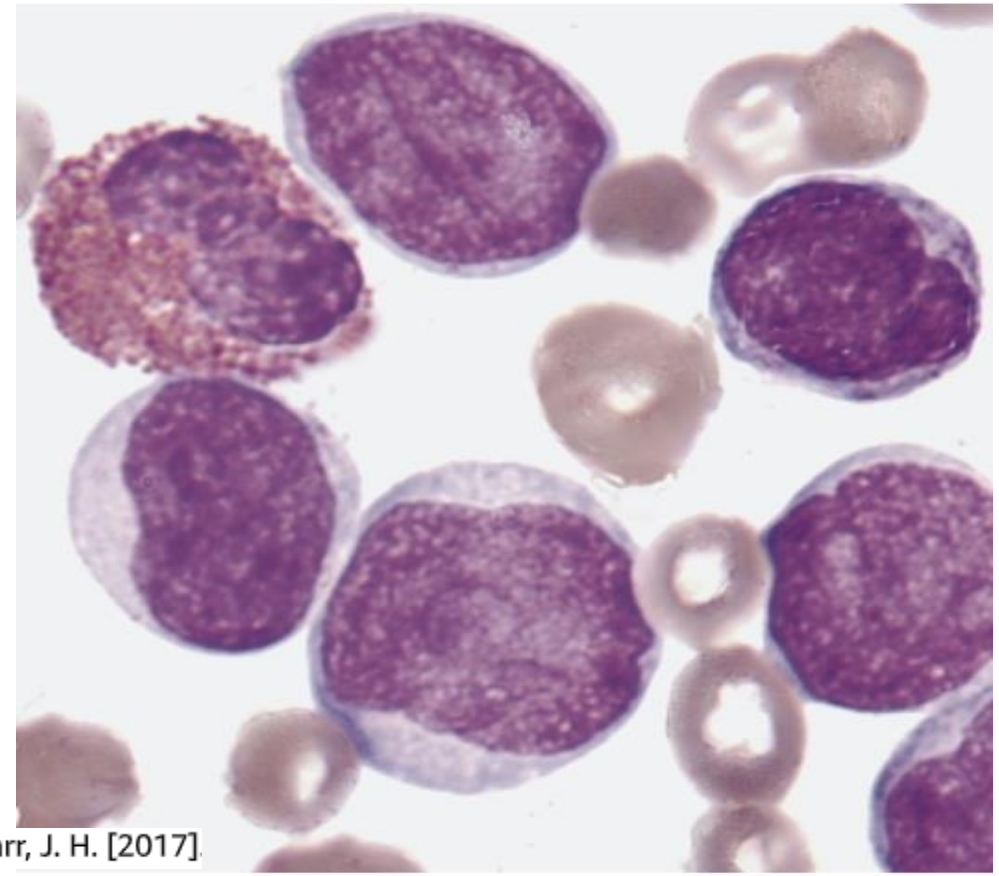
Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

AML with Recurrent genetic Abnormalities

- Diagnosis based on genetic abnormality regardless of blast count
- Good prognosis
  - AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
    - FAB M4eo
  - Acute promyelocytic leukemia with PML-RARA
    - FAB M3

AML with t(8;21) and inv(16)





From Rodak, B. F., & Carr, J. H. [2017]

AML with Recurrent genetic Abnormalities

- Poor prognosis translocations
  - AML with t(9:11)(p21.3;q23.3); *KMT2A-MLLT3*
  - AML with t(6:9)(p23;q34.1); *DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(3q21.3;q26.2); *GATA2, MECOM*
  - AML with t(1:22)(p13.3;q13.1); *RBM15-MKL1*
  - AML with *BCR-ABL1* (de novo)

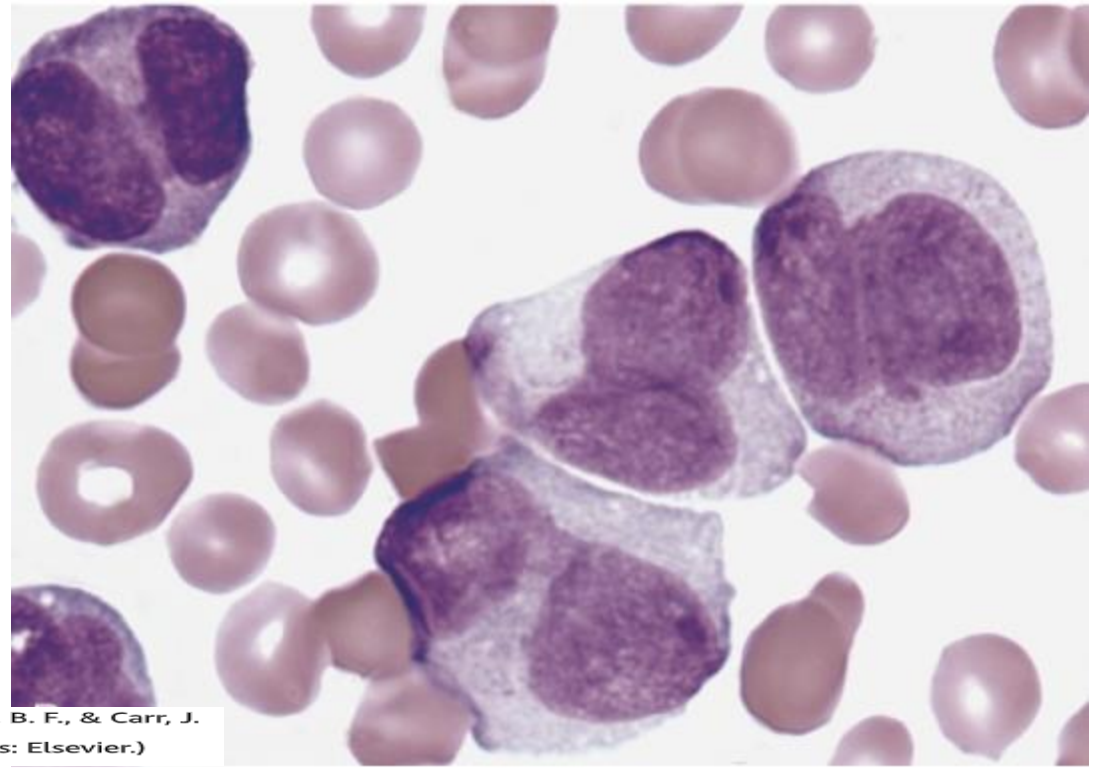
AML with Recurrent genetic Abnormalities Con't

- Additional entities with gene mutations
  - AML with mutated *NPM1* – favorable prognosis
  - AML with mutated *CEBPA*- favorable prognosis
  - AML with mutated *RUNX1*- not favorable prognosis

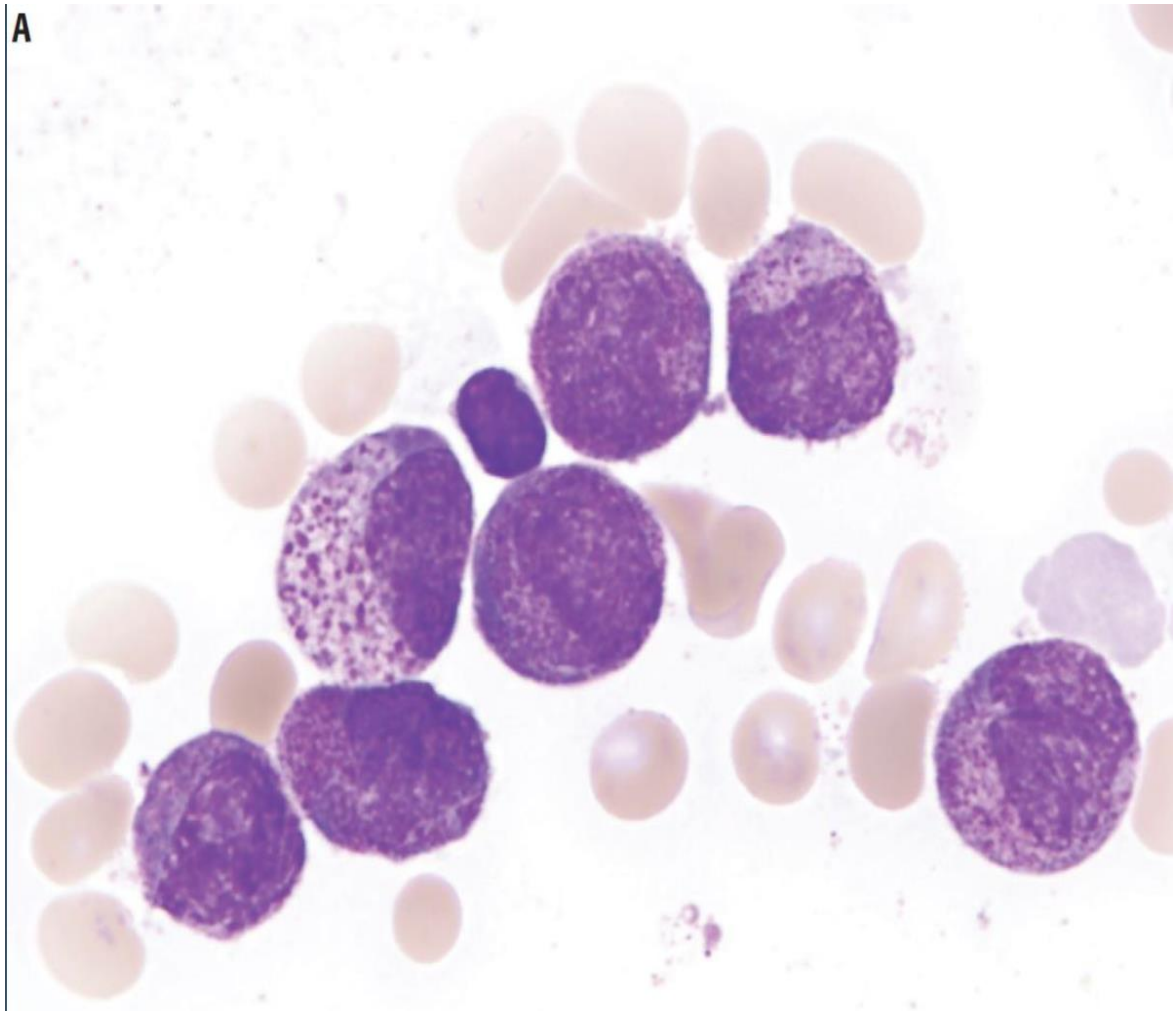
AML with t(15;17)(q22;q12);*PML-RARA*

- Abnormal promyelocytes with heavy granulations, sometimes obscuring the nucleus and abundant cytoplasm.
- Auer rods are frequently seen, and some cells may contain bundles or stacks of Auer rods.
- Often present with sign and symptoms of DIC
  - Prolonged PT, increased fibrin degradation products, and low fibrinogen
- PB smear almost always shows schistocytes, and marked thrombocytopenia
- Prognosis is excellent with ATRA and arsenic
  - Order STAT FISH

Acute Promyelocytic Leukemia



Source: (From Rodak, B. F., & Carr, J. *...las.* [5th ed.]. St. Louis: Elsevier.)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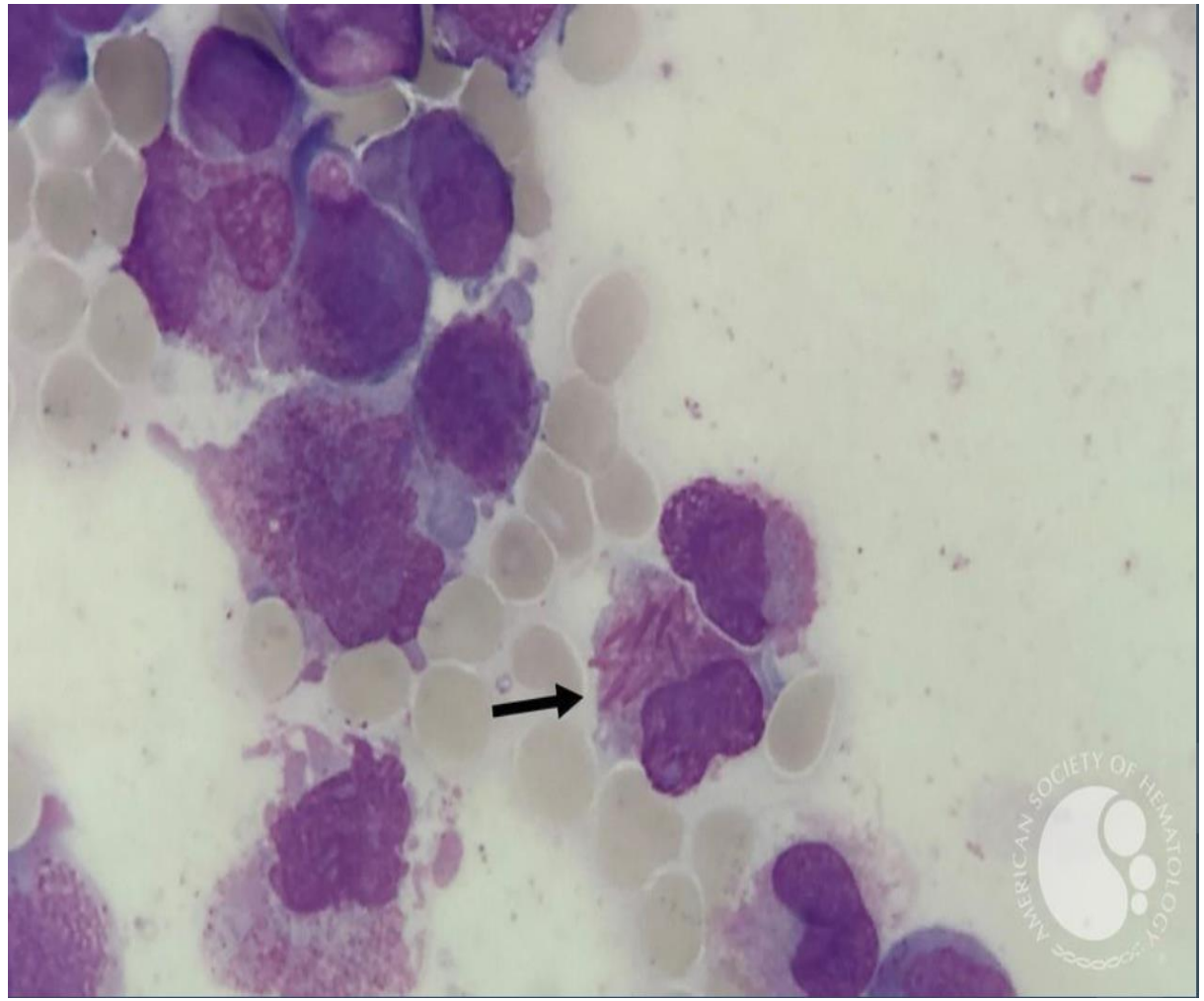
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AML with Myelodysplasia Related Changes

- Affects older adults and poor prognosis
- WHO 2016: 3 ways to make the diagnosis
  - AML arising from a prior MDS or MDS/MPN
  - AML with MDS-defining cytogenetic abnormalities, eg. -7/del(7q)
  - >50% dysplasia in at least two cell lineages
- Current classifications based on mutations/cytogenetics and history only

Therapy Related Myeloid Neoplasms

- t-MDS, t-AML and t-MDS/MPN
- Treatment related AML, MDS or MDS/MPN
  - Alkylating agents/radiation
  - Topoisomerase II inhibitors
- Poor prognosis regardless of blast count
- Used as dx modifier in ICC

AML not otherwise categorized

- Leukemia with features that do not fit into previously described categories
- Grouped according to morphology, flow cytometry and cytochemistry

Myeloproliferative Neoplasm (MPN)

- Clonal hematologic stem cells disorders characterized by proliferation in the marrow of one or more of the myeloid lineages.
- Relatively normal maturation

Chronic myeloid leukemia (CML)	Polycythemia vera (PV)
Primary myelofibrosis (PMF)	Essential thrombocythemia(ET)
Chronic neutrophil leukemia	Chronic eosinophilic leukemia
Myeloproliferative neoplasm, unclassifiable	

Myeloproliferative Neoplasm(MPN)

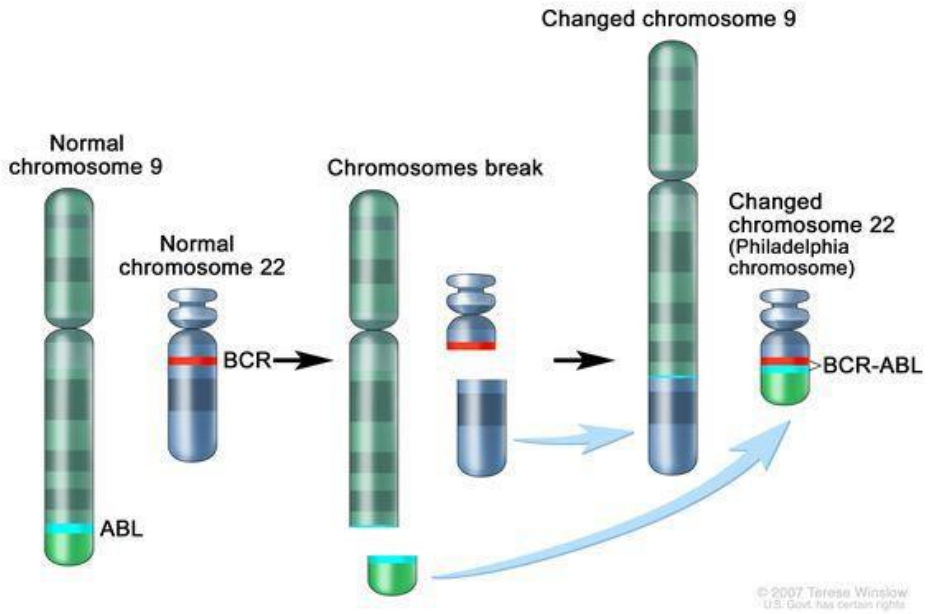
- Productive proliferation in the bone marrow → peripheral cytoses(except PMF)
- Philadelphia chromosome positive
  - CML unique with t(9;22)
- Philadelphia chromosome negative
  - PV ,ET and PMF (non CML MPN) often have mutations in *JAK2(V617F), CALR* or *MPL*
- Non-CML MPN can all lead to a stage with bone marrow fibrosis where eventually the patients develop cytopenias
- MPN can also develop increased blasts where blast stage (>19% blasts) is essentially AML

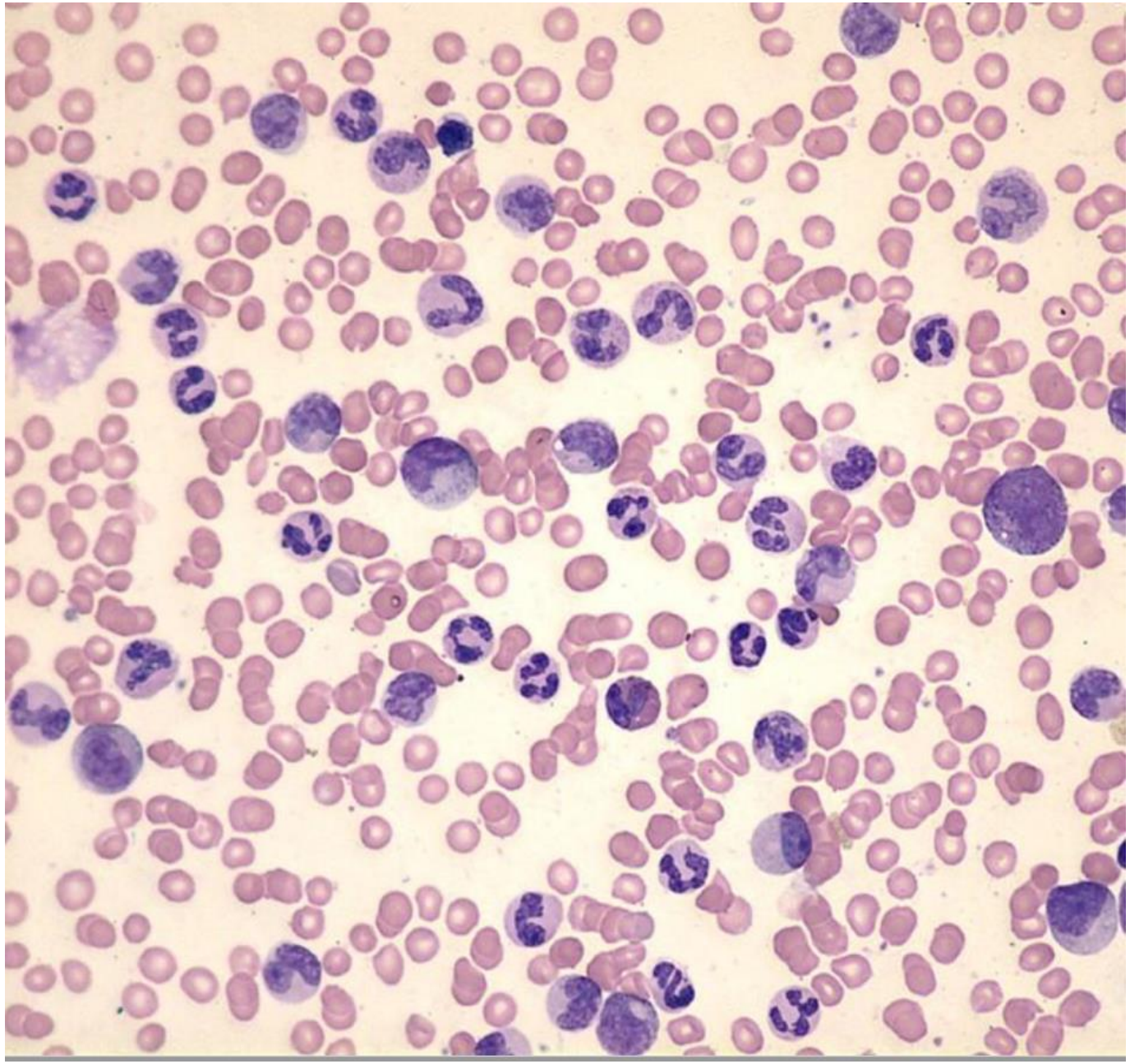
Chronic Myeloid Leukemia(CML)

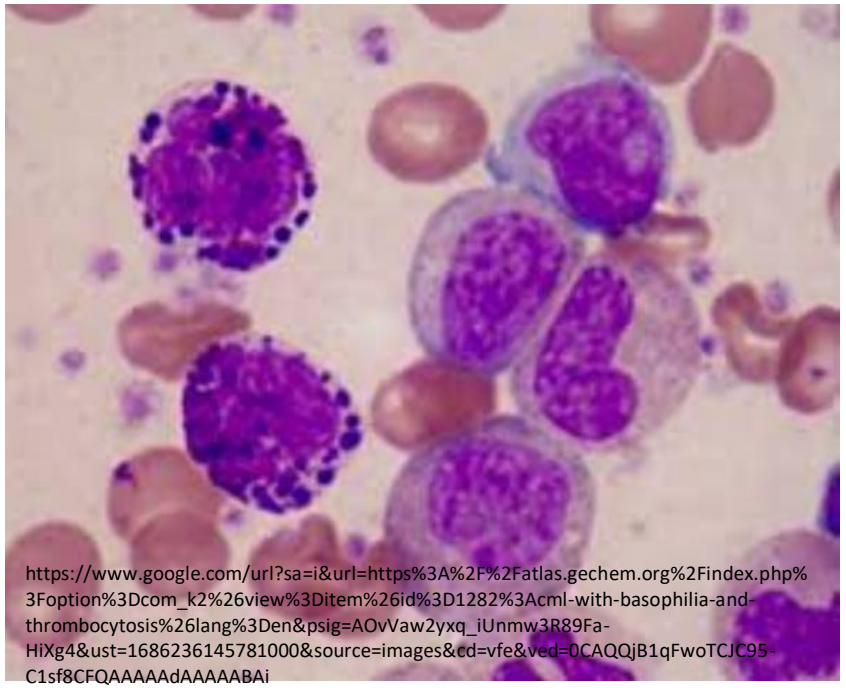
- CML is an MPN arising from a single genetic translocation in pluripotential HSC causing overproduction of myeloid cell line and their precursors
- It occurs at any age but predominantly seen in individuals aged 46 to 53 years
- Laboratory findings
  - Increased WBC count
  - Increased neutrophils and precursors in blood and bone marrow
  - May even produce few blasts
  - Basophilia and eosinophilia
  - Platelet count is often elevated

CML

- The first disease associated with a specific genetic defect, the “Philadelphia Chromosome” t(9;22)
- Fusion of 2 genes: BCR(chromosome 22) and ABL1 (on chromosome 9), resulting in BCR-ABL1 fusion gene
- Produce BCR-ABL1 fusion protein, a dysregulated tyrosine kinase
- Targeted drugs against ABL tyrosine kinase greatly improve outcomes
  - Imatinib(Gleevec), nilotinib, dasatinib, etc







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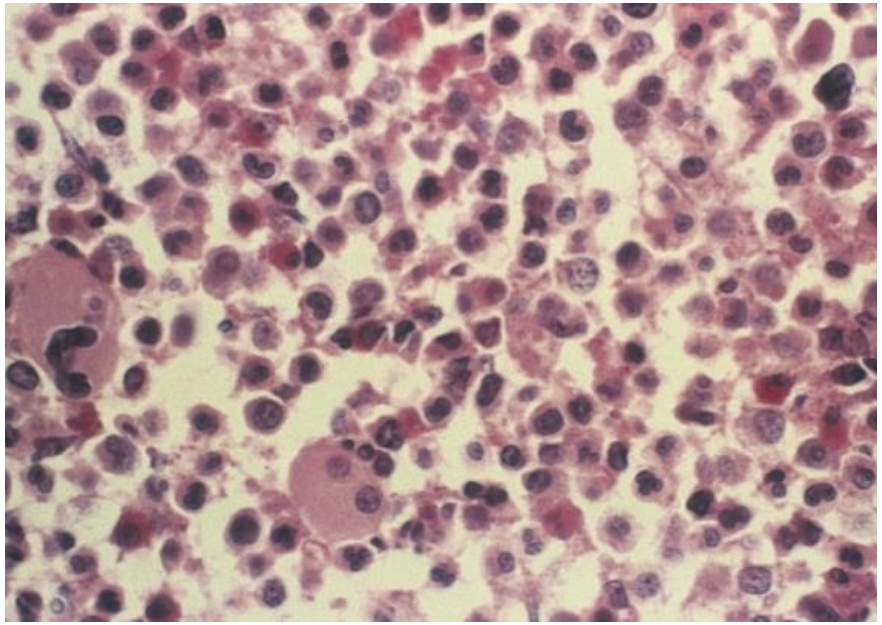


CML

- Leukocyte alkaline phosphate enzyme activity may aid in initial preliminary differentiation of CML from leukemoid reaction

Polycythemia Vera (PV)

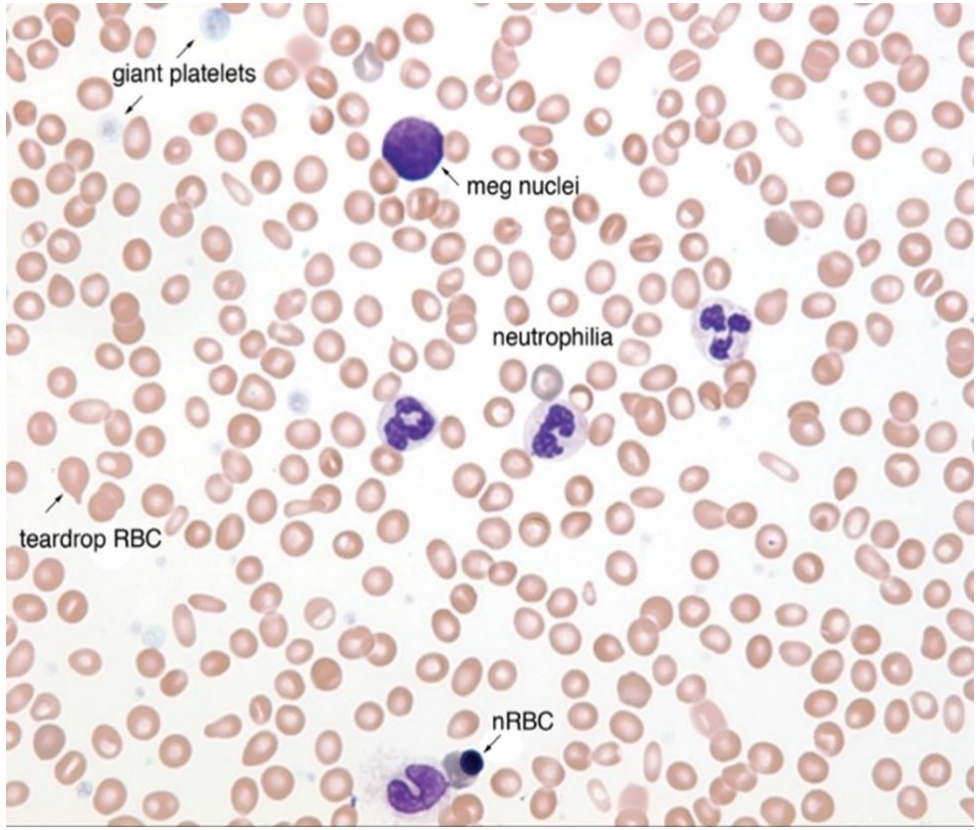
- It is a neoplastic clonal MPN characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis.
- Diagnostic features:
  - Increased HGB, Hct, Red cell mass (HB >16.5 g/dl in men, > 16.0 g/dl in women)
  - Hypercellular bone marrow
  - No increase in serum erythropoietin level
- Splenomegaly and hepatomegaly
- >95 % of patients have *JAK2 V617F* mutation
- Can treat with *JAK2* inhibitors (ruxolitinib/Jakafi, etc)

Primary Myelofibrosis (PMF)

- Bone marrow fibrosis due to the proliferation of hematopoietic stem cells resulting in fibrosis
- Normal hematopoiesis is blocked in the BM as BM becomes more fibrotic
- Begins with a proliferative phase, but characteristic morphology of bizarre megakaryocytes present even before fibrosis
- Patients eventually develop pancytopenia as the marrow fills with reticulin, then collagen, fibrosis, often resulting in “dry tap”

Primary Myelofibrosis (PMF)

- Extra medullary hematopoiesis causes hepatosplenomegaly and leukoerythroblastosis
  - Circulating nRBCs, immature cells/blasts, and teardrop shaped RBC's
- Survival rate depends on stage at diagnosis, fibrotic stage average survival 3-7 years



Essential Thrombocythemia (ET)

- Clonal proliferation of megakaryocytes in BM
- Characterized by increase platelets and megakaryocytic hyperplasia
- PB Platelet count ≥450k (can be >1 million), non-specific
- Asymptomatic, usually discovered on routine CBC
- Complications are hemorrhage/thrombosis
- Treatment: ASA, hydroxyurea, *JAK* inhibitors

Other MPN

- Chronic neutrophilic leukemia- *CSF3R* mutations
- Chronic eosinophilic leukemia
- MPN, U

- Also mastocytosis

Myelodysplastic Syndromes (MDS)

- Clonal stem cell disorder resulting from a lesion in the stem cell that leads to increased INEFFECTIVE hematopoiesis
  - Bone marrow is typically hypercellular BUT
  - Peripheral counts are DECREASED (cytopenias)
- MDS is a disease of elderly ; the median age of diagnosis >70 yrs.
- Typically also morphologic dysplasia but might only see increased blasts <20%

Myelodysplastic Syndromes (MDS)

- Categorized by
  - Number of dysplastic lineages: single lineage dysplasia (SLD), multilineage dysplasia (MLD)
  - Presence or absence of ring sideroblasts (*SF3B1*): MDS with ring sideroblasts and SLD/MLD
  - Presence of increased blasts: MDS-excess blasts 1 (PB 2-4%, BM 5-9%) NO Auer rods, MDS-excess blasts 2 (PB 5-19%, BM 10-19%) or WITH Auer rods
  - Presence of isolated del(5q)
  - Pediatric MDS

Myelodysplastic Syndromes (MDS)

- Symptoms are related to cytopenias, worst outcome is transformation to AML
- Outcome heavily influenced by % blasts and cytogenetics
  - Very good: -Y, del(11q)
  - Good: normal, del (5q), del(20q) etc
  - Intermediate: del(7q), +8, +19, iso17q, etc
  - Poor: -7, inv(3), t(3;3), del (3q), complex (3 abnormalities)
  - Very poor: >3 abnormalities

Myelodysplastic Syndromes (MDS)

- Low grade disease can be treated supportively: transfusions and growth factors to correct cytopenias
- Higher grade disease requires therapy with chemo or other agents
- Very bad prognosis disease may go to stem cell transplant

MDS/MPN overlap disorders

- Clonal stem cell disorders with both proliferative and dysplastic features
  - Chronic myelomonocytic leukemia
  - Atypical chronic myeloid leukemia, *BCR-ABL1*-negative
  - Juvenile myelomonocytic leukemia
  - MDS/MPN with ring sideroblasts and thrombocytosis
  - MDS/MPN, U

References

Rodak’s Hematology, Clinical Principles and Applications 6th Edition

Additional material courtesy of Dr. Megan Nakashima, MD