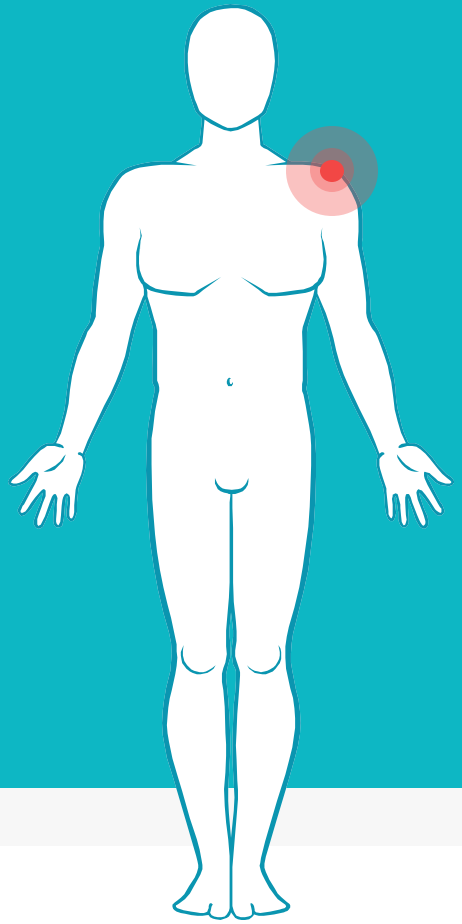
Hematopoietic & Lymphoid System

White Cell disorders



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2.
Neoplastic Proliferations of White Cells

~ Myeloid Neoplasms

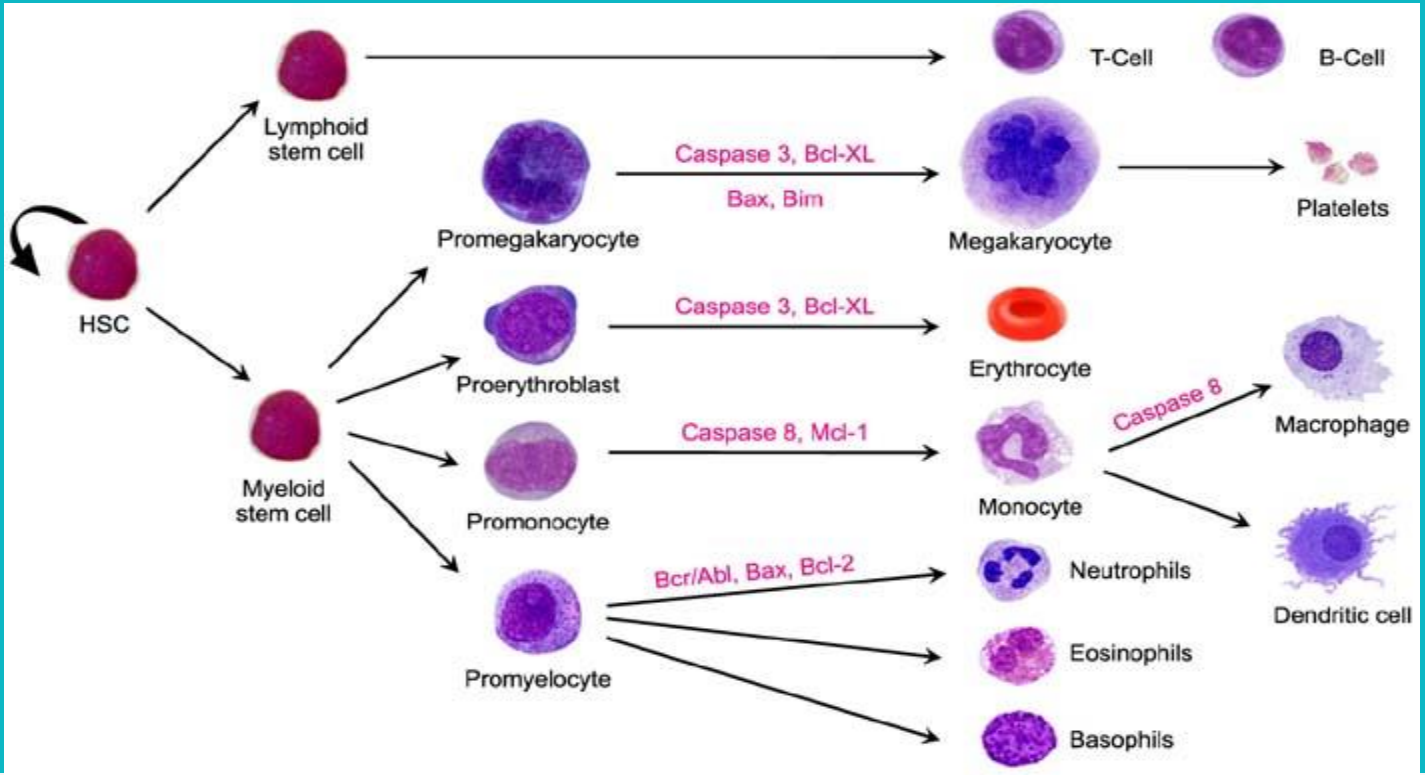
Myeloid Neoplasms

- Neoplasms originated from hematopoietic progenitors.
- Primarily involve the bone marrow & replace normal marrow elements.
- Lesser secondary Hematopoietic organs involvement (LN , spleen & liver).

Myeloid Neoplasms

Three broad categories of myeloid neoplasia:

- **Acute myeloid leukemia (AML):** neoplastic cells are blocked at an early stage of development → Immature myeloid cells (blasts) accumulate in BM & frequently circulate in PB.
- **Myeloproliferative neoplasms (MPN):** neoplastic clone continues to terminal differentiation but with increased or dysregulated growth.
- **Myelodysplastic syndromes (MDS):** terminal differentiation occurs but in a disordered and ineffective fashion → dysplastic BM precursors & PB cytopenias.



Acute myeloid leukemia (AML)

Acute myeloid leukemia (AML)

- Affects all age group, peak > 60 years.
- Clinical signs & symptoms; result from the replacement of normal marrow elements by leukemic blasts; symptoms related to anemia, thrombocytopenia, & neutropenia.
- Acute: present within a few weeks of the onset of symptoms.
- Splenomegaly & lymphadenopathy are less prominent than in ALL (Acute Lymphoblastic leukemia)

Acute myeloid leukemia (AML)

- Increase age.
- Male sex
- Previous cancer treatment.
- Exposure to radiation. such as survivors of a nuclear reactor accident.
- Dangerous chemical exposure. Exposure to certain chemicals, such as benzene.
- Smoking. AML is linked to cigarette smoke, which contains benzene and other chemicals.
- Other blood disorders.
- Genetic disorders, Down syndrome

Acute myeloid leukemia (AML) – Pathogenesis

- Most AMLs harbor mutations in genes encoding transcription factors that are required for normal myeloid cell differentiation → interfere with the differentiation of early myeloid cells → accumulation of myeloid precursors (blasts) in BM.
- **Examples:** t(15;17) in acute promyelocytic Leukemia (APL) → fusion of retinoic acid receptor α (RARA) gene on chr. 17 & PML gene on chr. 15 → PML/RARA fusion protein → blocks myeloid differentiation at promyelocytic stage.

Acute myeloid leukemia (AML) – Pathogenesis

- Treatment with all-trans retinoic acid (**ATRA**), an analogue of vitamin A, overcome this block → induce the neoplastic promyelocytes to differentiate into neutrophils rapidly → clears the tumor.
- The effect is very specific; AMLs without t(15;17) don't respond to ATRA.
- This is an important example of a highly effective therapy targeted at a tumor-specific molecular defect.
- t(15;17) AML have the best prognosis of any type → curable in > 80%

Acute myeloid leukemia (AML) – Classification

- AMLs are very diverse in terms of genetics, cellular lineage, and degree of maturation.
- WHO classification relies on all of these features to divide AML into four categories:

(1) AMLs ass with specific genetic aberrations: important coz they predict outcome & they guide therapy.
(2) AMLs with dysplasia: arise from MDSs.
(3) AMLs occurring after genotoxic chemotherapy.
(4) AMLs, Not otherwise specified: subclassified based on the predominant line of differentiation

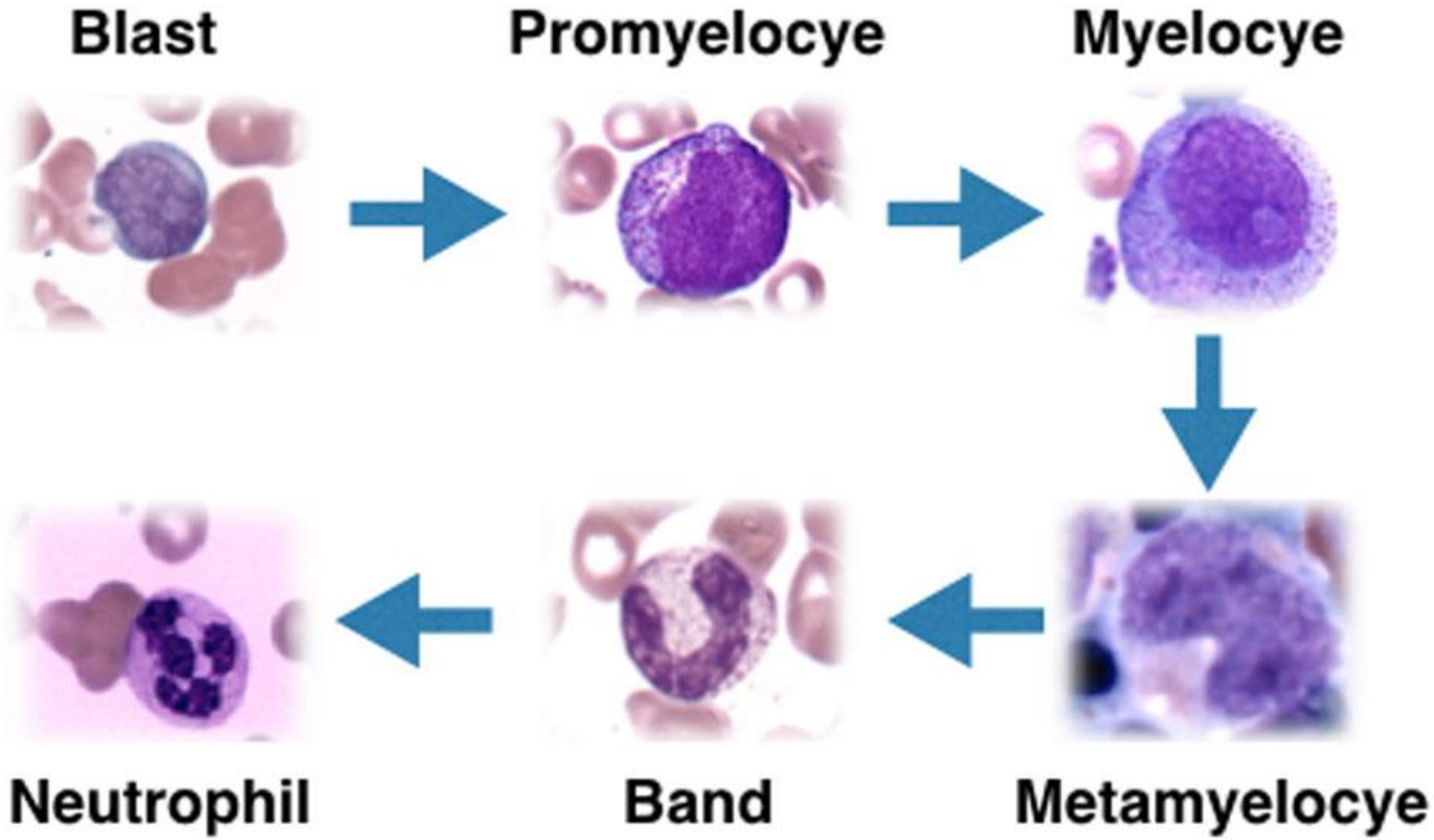
Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *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

TABLE 1. WHO classifications for AML subtypes

Type	Name
M0	Minimally differentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia (t(8;21)(q22,q22))
M2	Acute myeloblastic leukemia (t(6;9))
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4eo	Myelomonocytic leukemia with bone marrow eosinophilia
M5	• Acute monoblastic leukemia (M5a) • Acute monocytic leukemia (M5b)
M6	Acute erythroid leukemias, including —Erythroleukemia (M6a) —Very rare pure erythroid leukemia (M6b)
M7	Acute megakaryoblastic leukemia
M8	Acute basophilic leukemia

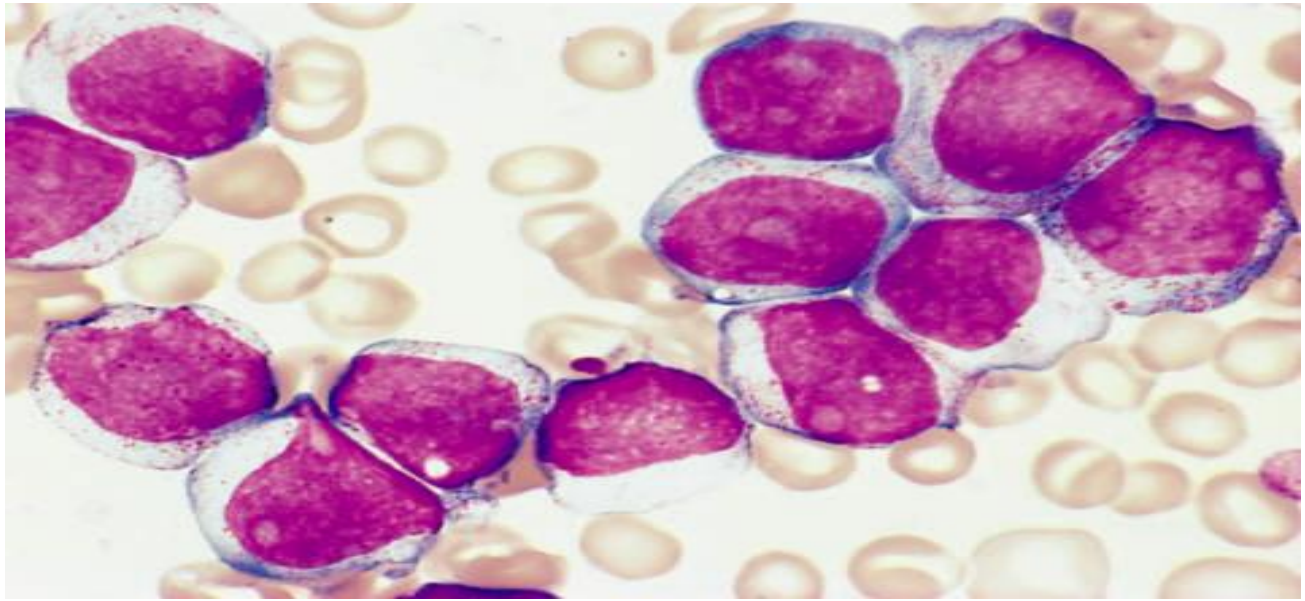
Key: AML, acute myeloid leukemia; t, translocation; WHO, World Health Organization.

Source: Acute myeloid leukemia classification. News-Medical.net Web site. http://www.news-medical.net/health/Acute-Myeloid-Leukemia-Classification.aspx. Accessed March 9, 2012.


Blast
Promyelocye
Myelocye
Neutrophil
Band
Metamyelocye

Acute myeloid leukemia (AML) – Morphology

- By definition → AML: the presence of at least 20% myeloid blasts or promyelocytes of BM cellularity.



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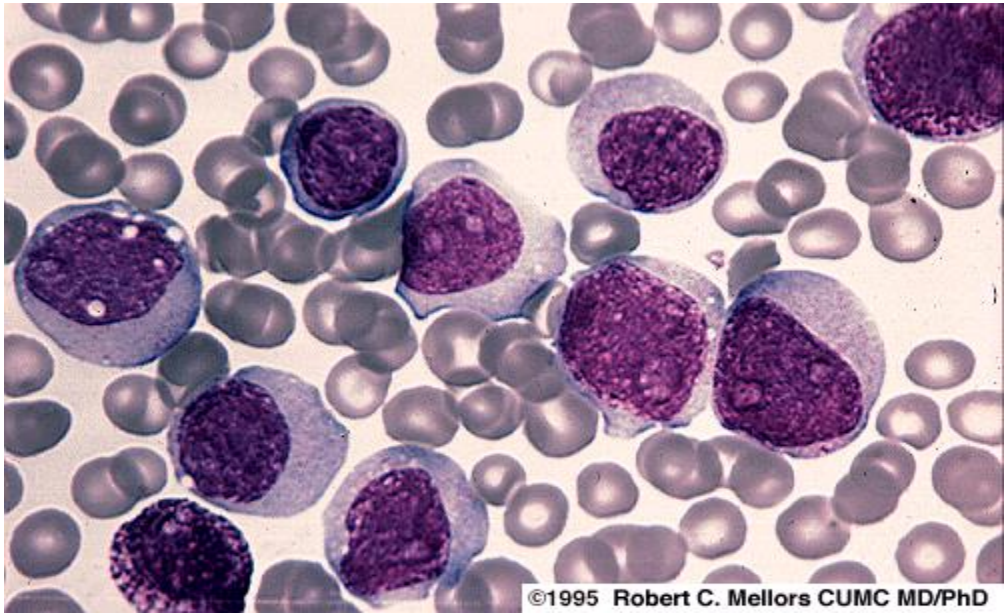
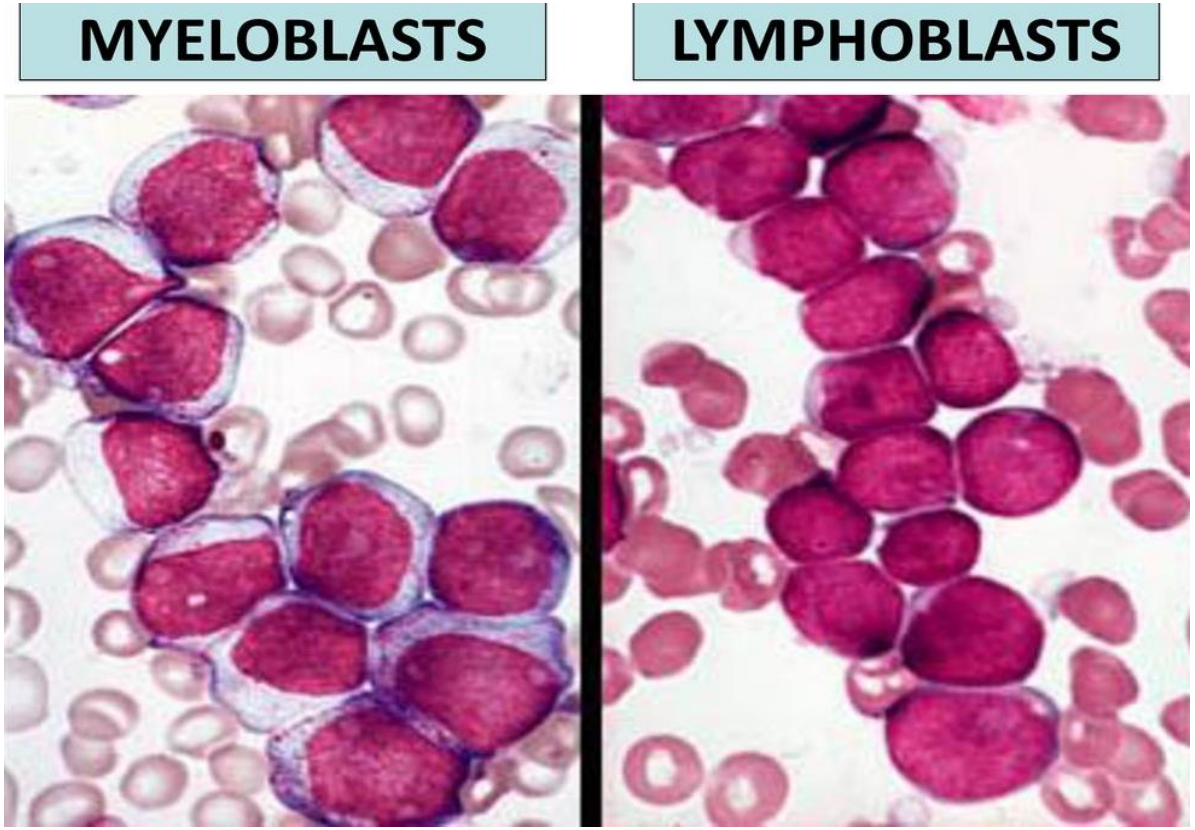


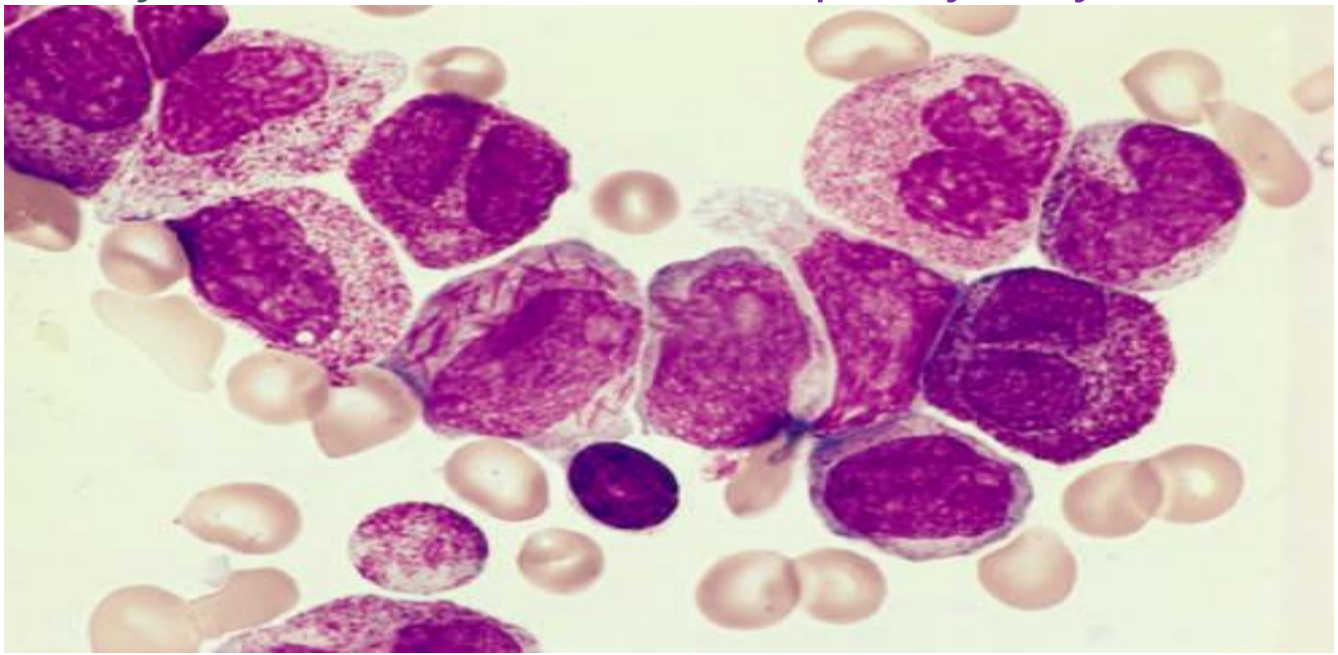
Acute myeloid leukemia (AML) – Morphology

Myeloblasts: have delicate nuclear chromatin, 2-4 nucleoli, larger cytoplasm than lymphoblasts & fine azurophilic cytoplasmic granules.



Acute myeloid leukemia (AML) – Morphology

Auer rods: distinctive red-staining needle-like azurophilic granules, present in many cases. Numerous in acute promyelocytic leukemia (APL).

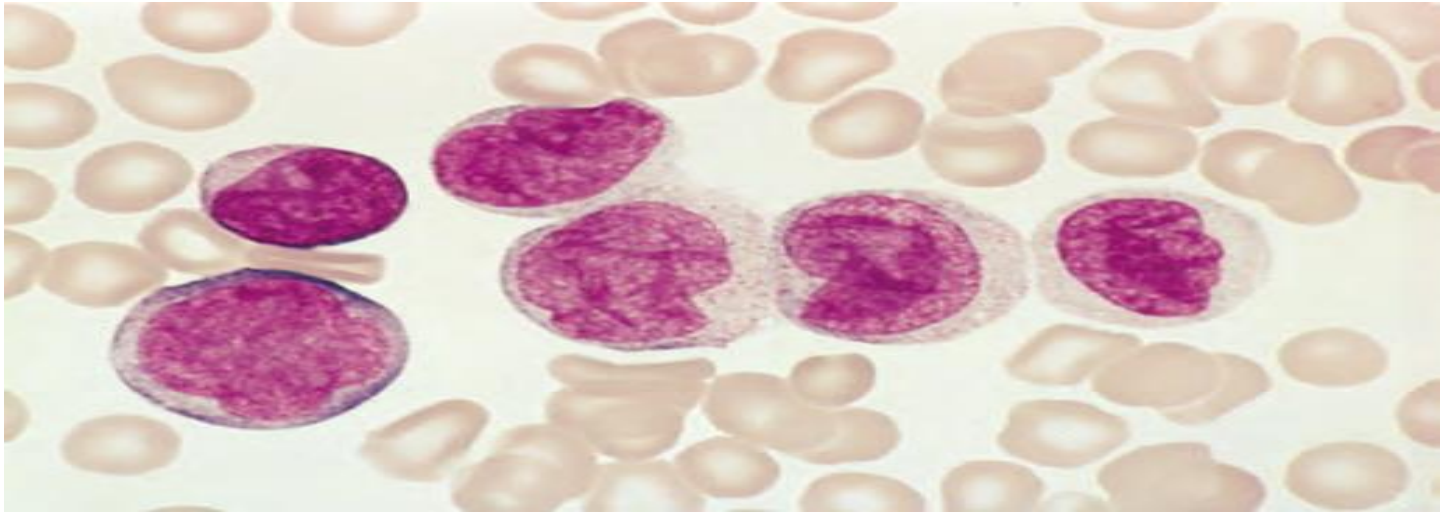


Acute myeloid leukemia (AML) – Morphology

- In other subtypes of AML, monoblasts, erythroblasts, or megakaryoblasts predominate.
- Occasionally, blasts are entirely absent from PB (aleukemic leukemia).
- For this reason, BM examination is essential to exclude acute leukemia in pancytopenic patients.

Acute myeloid leukemia (AML) – Morphology

- Monoblasts: have folded or lobulated nuclei, lack Auer rods.



Acute myeloid leukemia (AML) - Immunophenotype

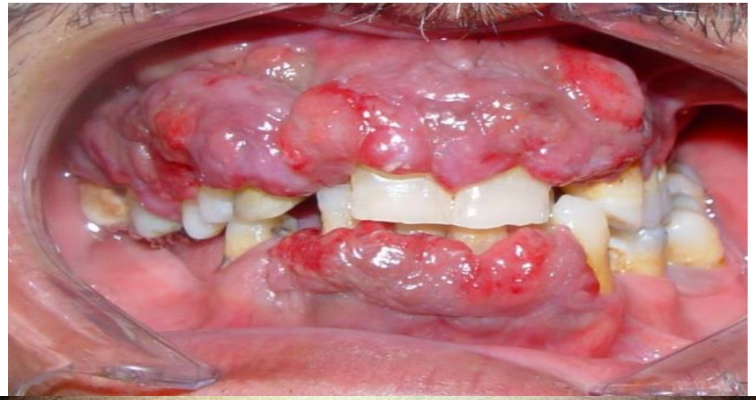
- Immunologic markers are heterogeneous in AML.
- Most tumors express some combination of myeloid-associated antigens; CD13, CD14, CD15, or CD117 (KIT).
- CD34: a marker of hematopoietic stem cells & often present on myeloblasts.
- Myeloperoxidase (MPO) , most specific.
- Such markers are helpful in distinguishing AML from ALL and in identifying AMLs with only minimal differentiation.

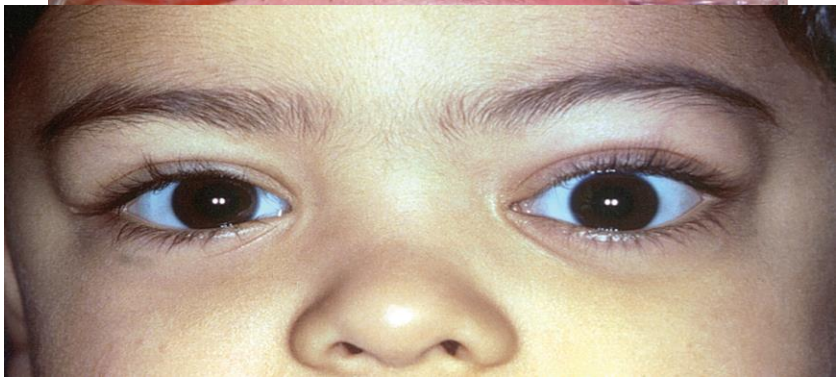
Acute myeloid leukemia (AML) - Clinical features

- Patients present within weeks or a few months of the onset of symptoms.
- Symptoms of anemia, neutropenia, & thrombocytopenia, (fatigue, fever, and spontaneous mucosal & cutaneous bleeding).
- CNS manifestations are less frequent than ALL.
- Procoagulants and fibrinolytic factors released by leukemic cells, especially in AML with the t(15;17) → **high DIC incidence.**

Acute myeloid leukemia (AML) – Clinical features

- Tumors with monocytic differentiation often infiltrate the skin (**leukemia cutis**) & the gingiva.
- AML occasionally presents as a localized soft-tissue mass → myeloblastoma or **granulocytic sarcoma**





Acute myeloid leukemia (AML) – Prognosis

- AML remains a devastating disease.
- Tumors with “good-risk” karyotypic abnormalities (t[8;21], inv[16]) are associated with a 50% chance of long-term disease-free survival.
- Overall survival in all patients is only 15-30% with conventional chemotherapy.

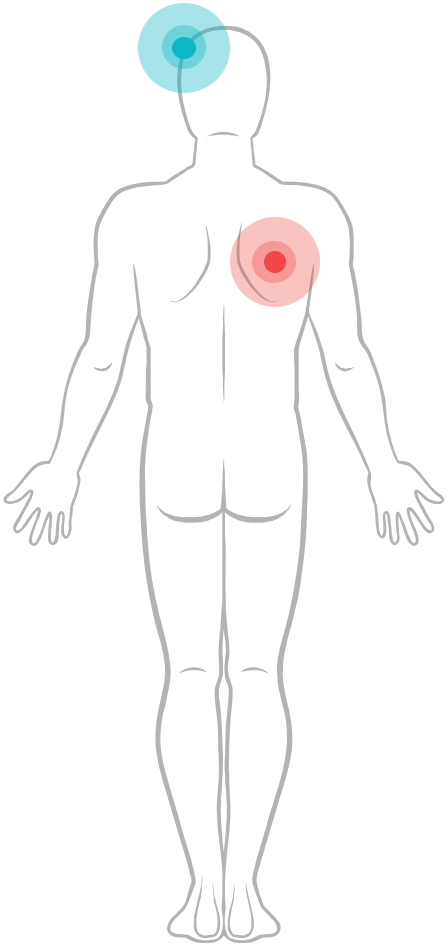
Acute vs Chronic leukemia

Acute leukemia

- Blasts
- Rapid proliferation of cells.
- Rapidly Fatal (<6 months without Tx)
- Lymphoid..ALL
- Myeloid … AML

Chronic leukemia

- Mature cells
- Gradual proliferation.
- More indolent disease. (2-6 years without Tx)
- Lymphoid … CLL
- MPN… CML



Questions?
Thank YOU!