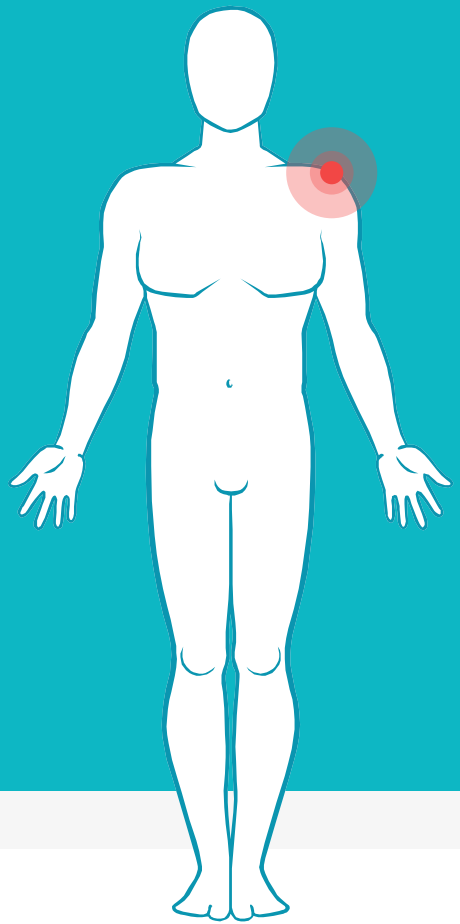
8/4/25

Hematopoietic & Lymphoid System

White Cell disorders



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Consultant hematopathologist
4/8/2025

2.
Neoplastic Proliferations of White Cells

~ Myeloid Neoplasms

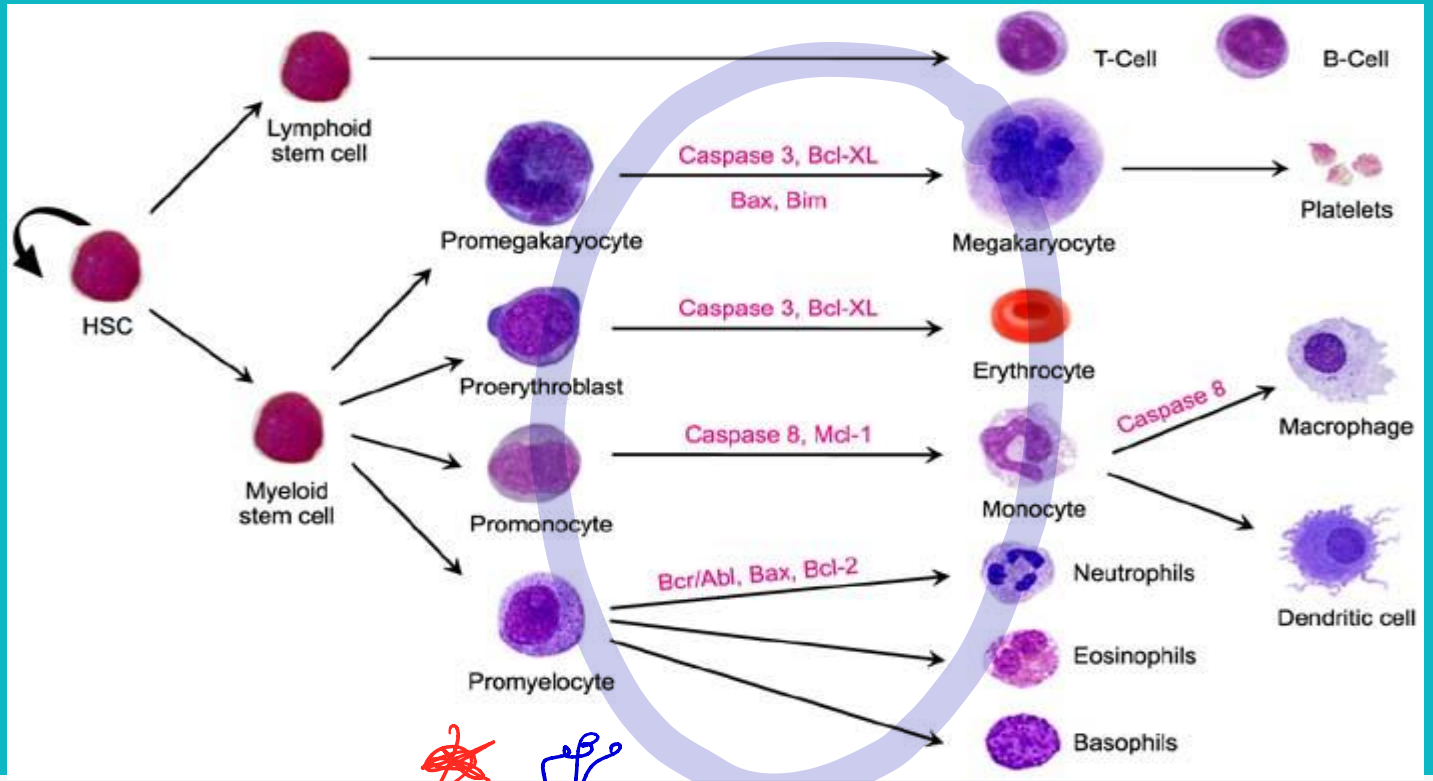
Myeloid Neoplasms

- 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.



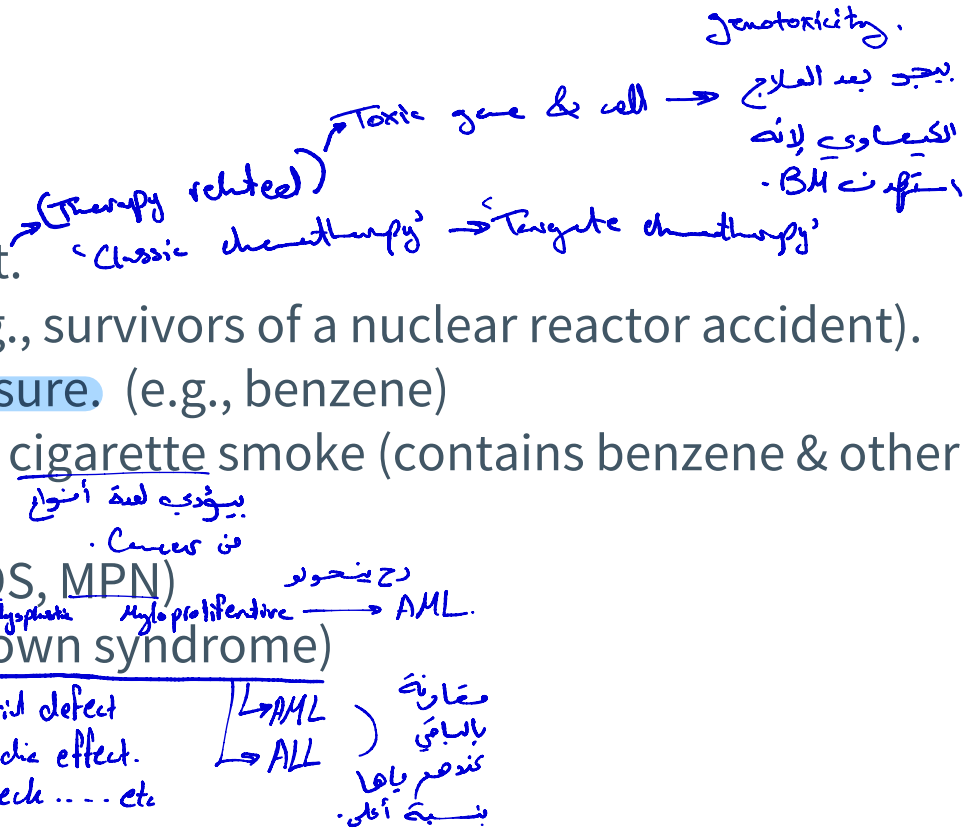
Acute myeloid leukemia (AML)

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)

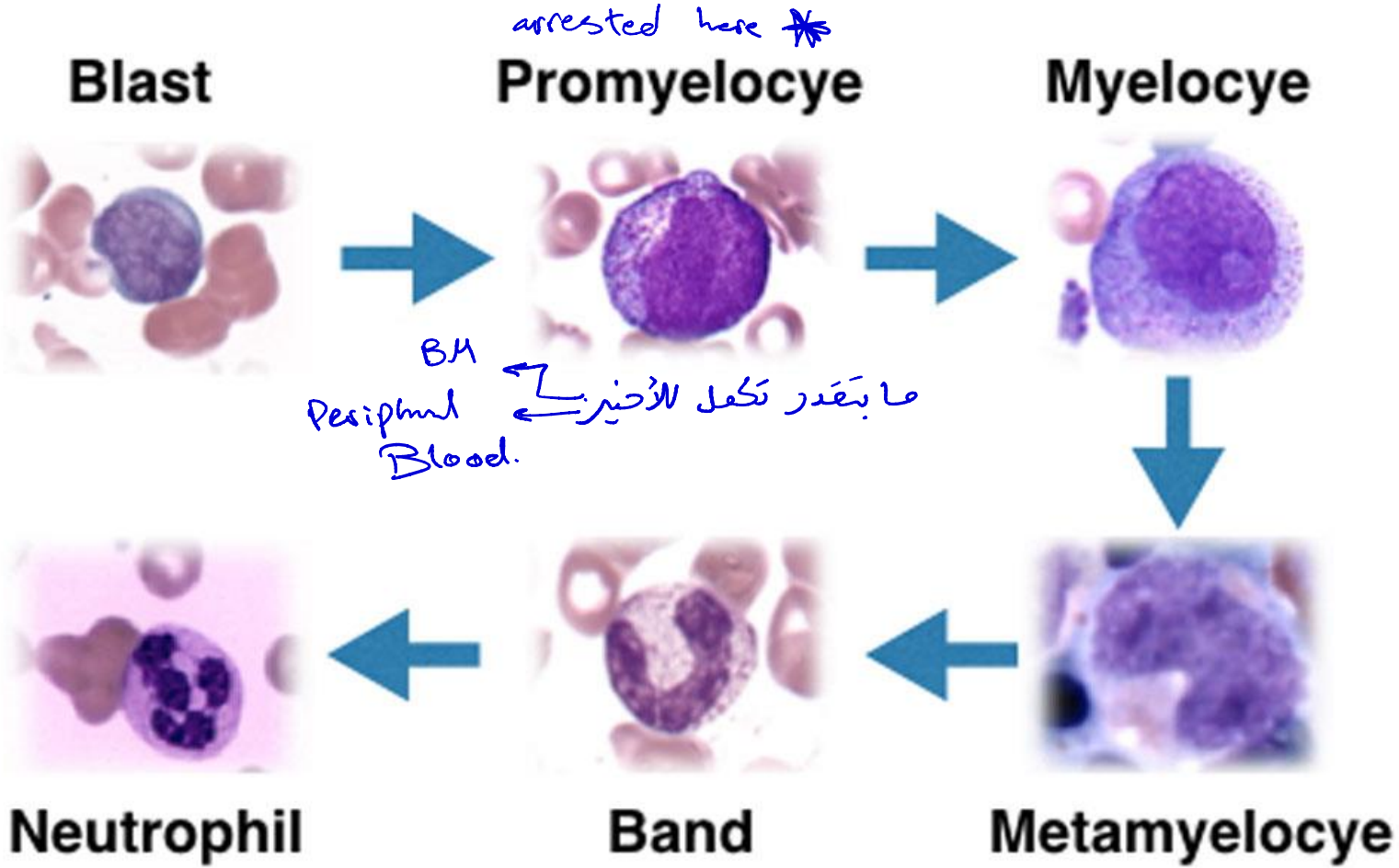
Acute myeloid leukemia (AML) – Risk factors

- Increase age.
- Male sex
- Previous cancer treatment.
- Exposure to radiation. (e.g., survivors of a nuclear reactor accident).
- Dangerous chemical exposure. (e.g., benzene)
- Smoking; AML is linked to cigarette smoke (contains benzene & other chemicals)
- Other blood disorders (MDS, MPN)
- Genetic disorders. (e.g., 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.


arrested here
Blast
Promyelocye
Myelocye
BM
Periphral Blood.
ما بتقدر تكمل للأخير
Neutrophil
Band
Metamyelocye

Acute myeloid leukemia (AML) – Pathogenesis

- Treatment with all-trans retinoic acid (**ATRA**), an analogue of vitamin A, overcomes 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 > 90%

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

Classification / Category → متغيرات

هو مطلوب

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.

Table 12.11 WHO Classification of AML

favorable مطلوب

Class	Prognosis
I. AML With Recurrent Chromosomal Translocations	
AML with t(8;21)(q22;q22); *RUNXT1/RUNX1* fusion gene	Favorable
AML with inv(16)(p13;q22); *CBFB/MYH11* fusion gene	Favorable
AML with t(15;17)(q22;q21.1); *PML/RARA* fusion gene	Favorable
AML with t(11q23;variant); *MLL* fusion genes	Poor
AML with mutated *NPM1*	Variable
II. AML With Multilineage Dysplasia	
With previous MDS	Very poor
Without previous MDS	Poor
III. AML, Therapy-Related	
Alkylating agent–related	Very poor
Epipodophyllotoxin-related	Very poor
IV. AML, Not Otherwise Classified	
Subclasses defined by extent and type of differentiation (e.g., myelocytic, monocytic)	Intermediate

Prognosis is included

Acute myeloid Leukemia

History

Chemotherapy ± Radiotherapy →

Myeloid neoplasm post cytotoxic therapy
(e.g. AML with *KMT2A::MLLT3* fusion post cytotoxic therapy)

AML with defining genetic abnormalities

Acute promyelocytic leukemia with *PML::RARA* fusion
AML with *RUNX1::RUNX1T1* fusion
AML with *CBFB::MYH11* fusion
AML with *DEK::NUP214* fusion
AML with *RBM15::MRTFA* fusion
AML with *BCR::ABL1* fusion
AML with *KMT2A* rearrangement
AML with *MECOM* rearrangement
AML with *NUP98* rearrangement
AML with *NPM1* mutation
AML with *CEBPA* mutation

MDS or MDS/MPN → AML, myelodysplasia-related

AML with other defined genetic alterations

- AML with *RUNX1T3::GLIS2* fusion
- AML with *KAT6A::CREBBP* fusion
- AML with *FUS::ERG* fusion
- AML with *MNX1::ETV6* fusion
- AML with *NPM1::MLF1* fusion

AML defined by differentiation

AML with minimal differentiation
AML without maturation
AML with maturation
Acute basophilic leukemia
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia*
Acute megakaryoblastic leukemia

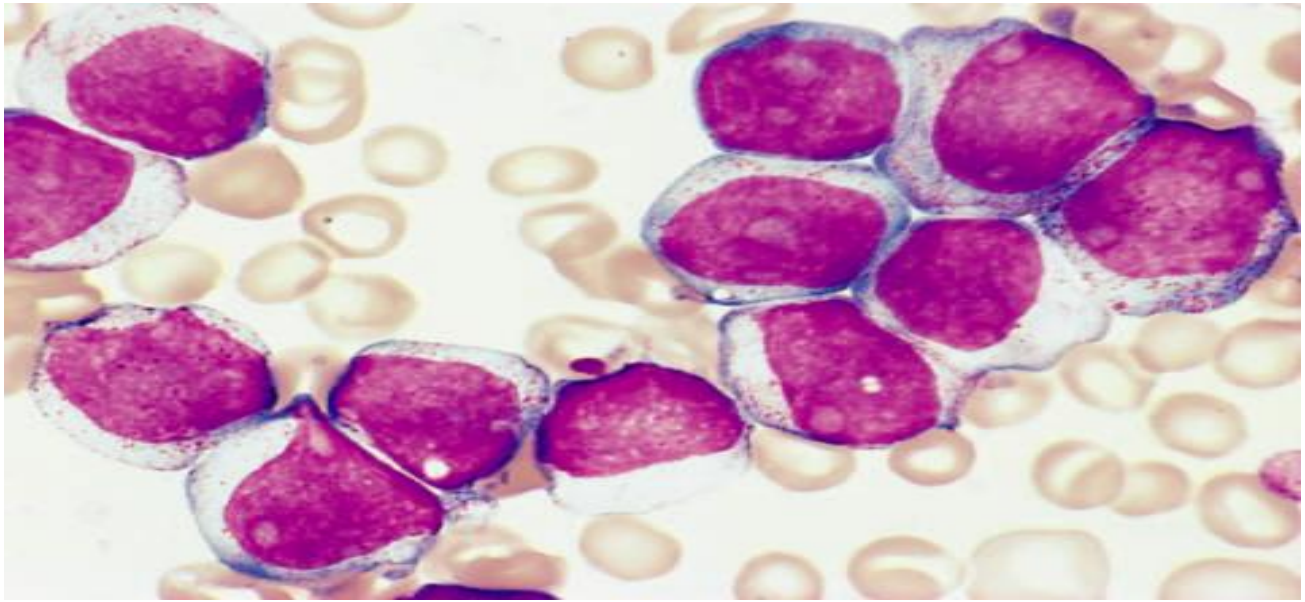
*the only type in this family that supersedes AML-MR

Acute myeloid leukemia (AML) – Morphology

- granules function ingest the captured cells from the macrophage.

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

- granules in the cytoplasm.



Acute myeloid leukemia (AML) – Morphology

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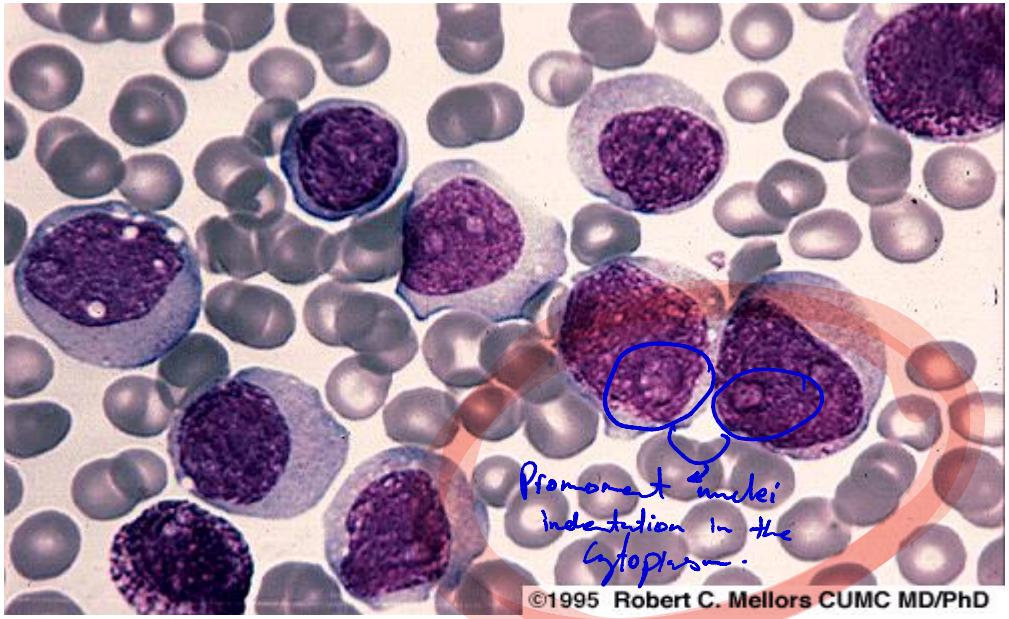
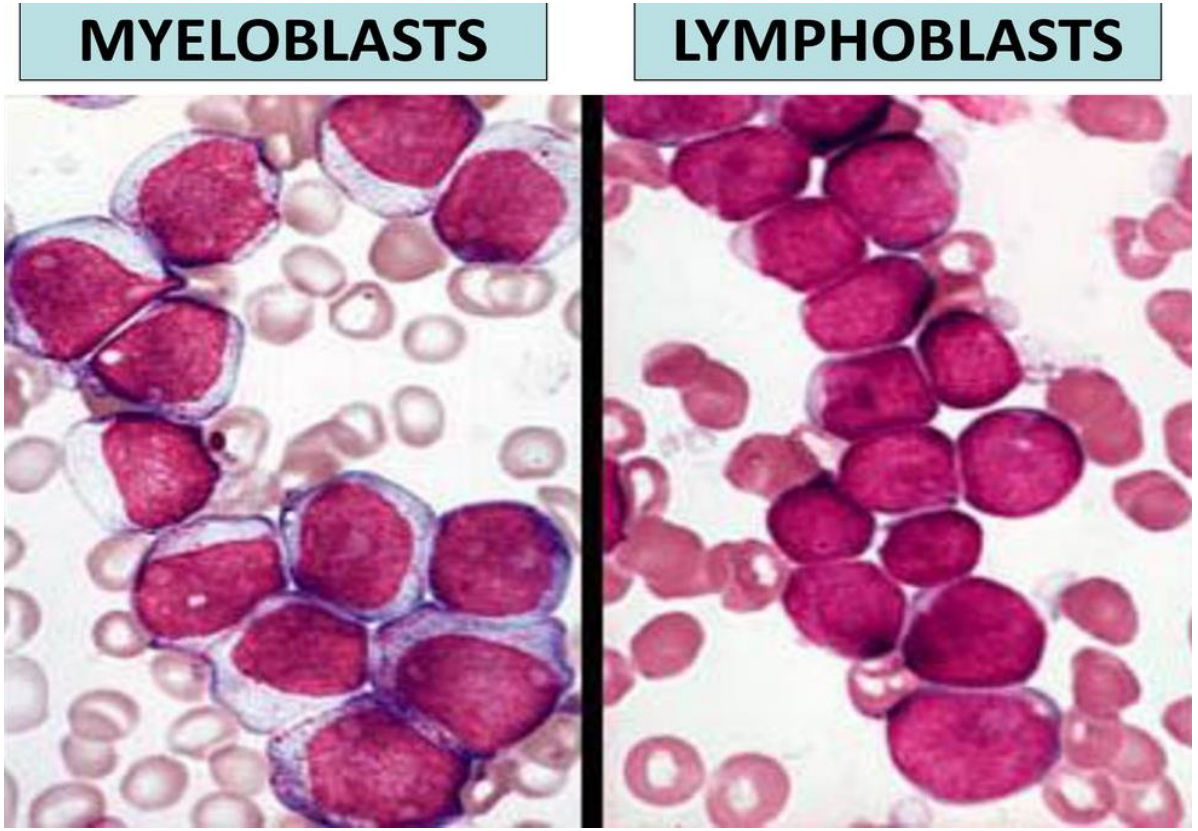


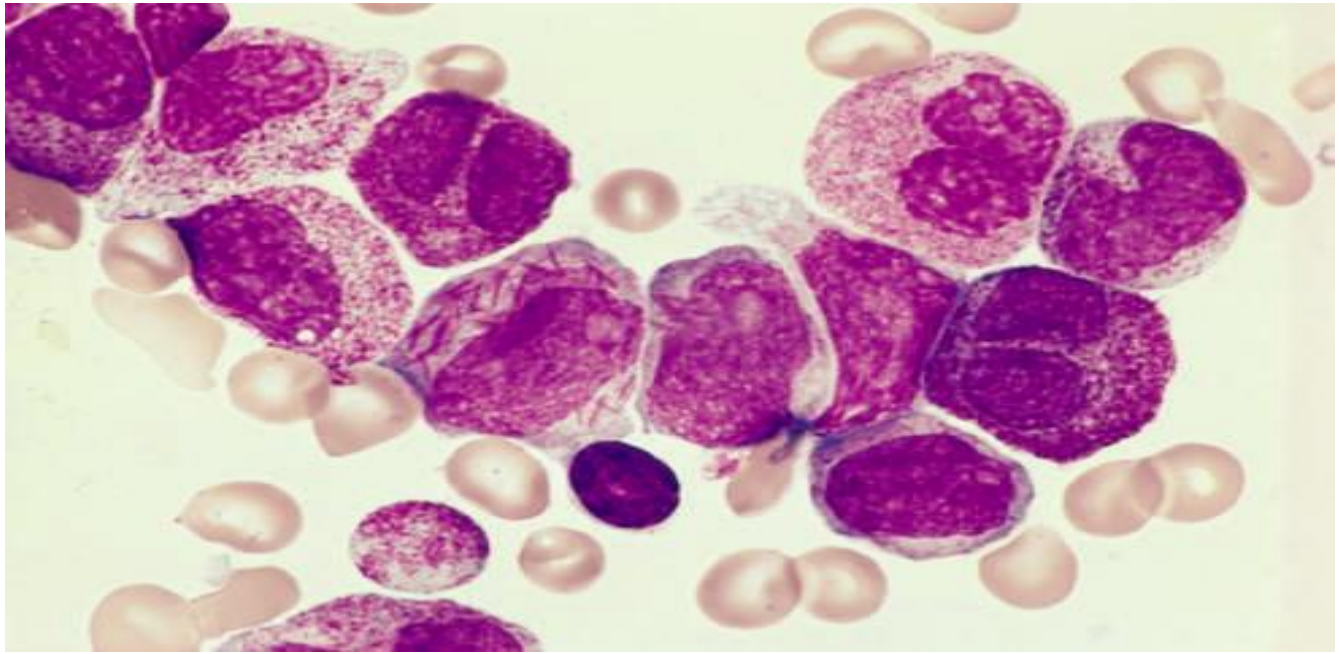
Acute myeloid leukemia (AML) – Morphology

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).

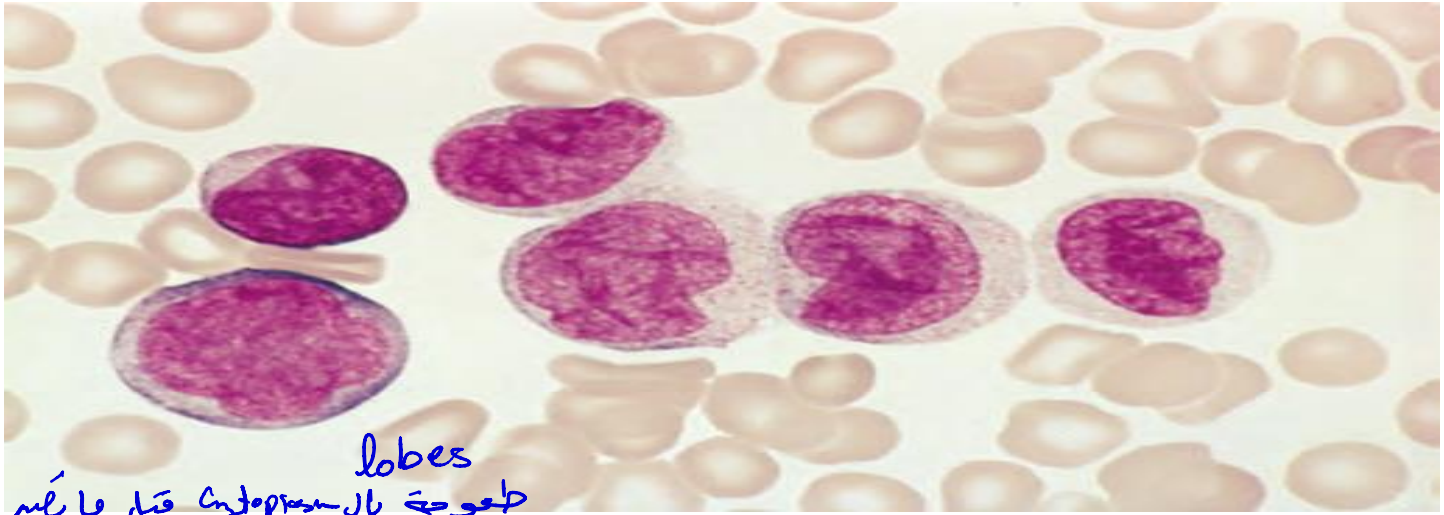


Acute myeloid leukemia (AML) – Morphology

- 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.



lobes

طعوجة بال Cytoplasm قبل ما تغير

فيقدر يشخصه لوكيميا.

kidney Shape

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

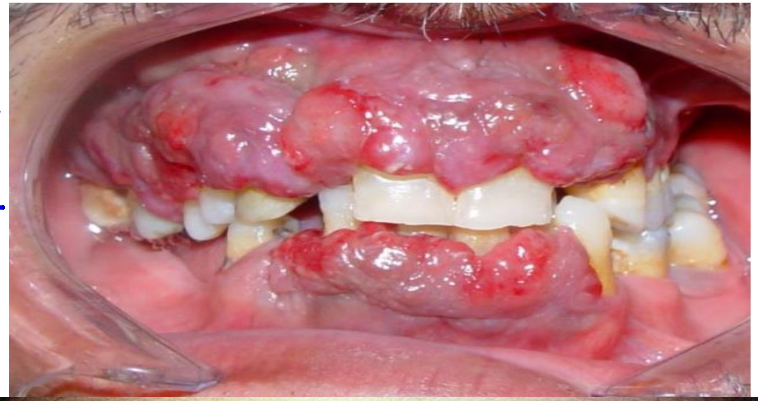
- Patients present within weeks or a few months of the onset of symptoms.
- Symptoms of anemia, neutropenia, & thrombocytopenia, (fatigue, fever, and spontaneous mucosal & cutaneous bleeding).
- CNS manifestations are less frequent than ALL.
- Procoagulants and fibrinolytic factors released by leukemic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

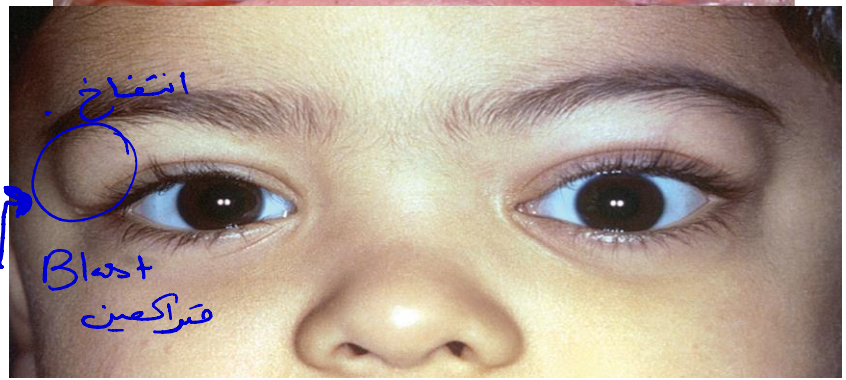
Can interact with the Anti-bodies. Immune syndromes

Bleeding عنده فيلبين

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.

كلهم الأنواع

inversion

يعني بتعرك جلد نفس
- gene

Bad prognosis

good ← t 17

إذا

Acute vs Chronic leukemia

Acute leukemia

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

بالعادة
medium survival
بكون مع العلاج.

Chronic leukemia

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