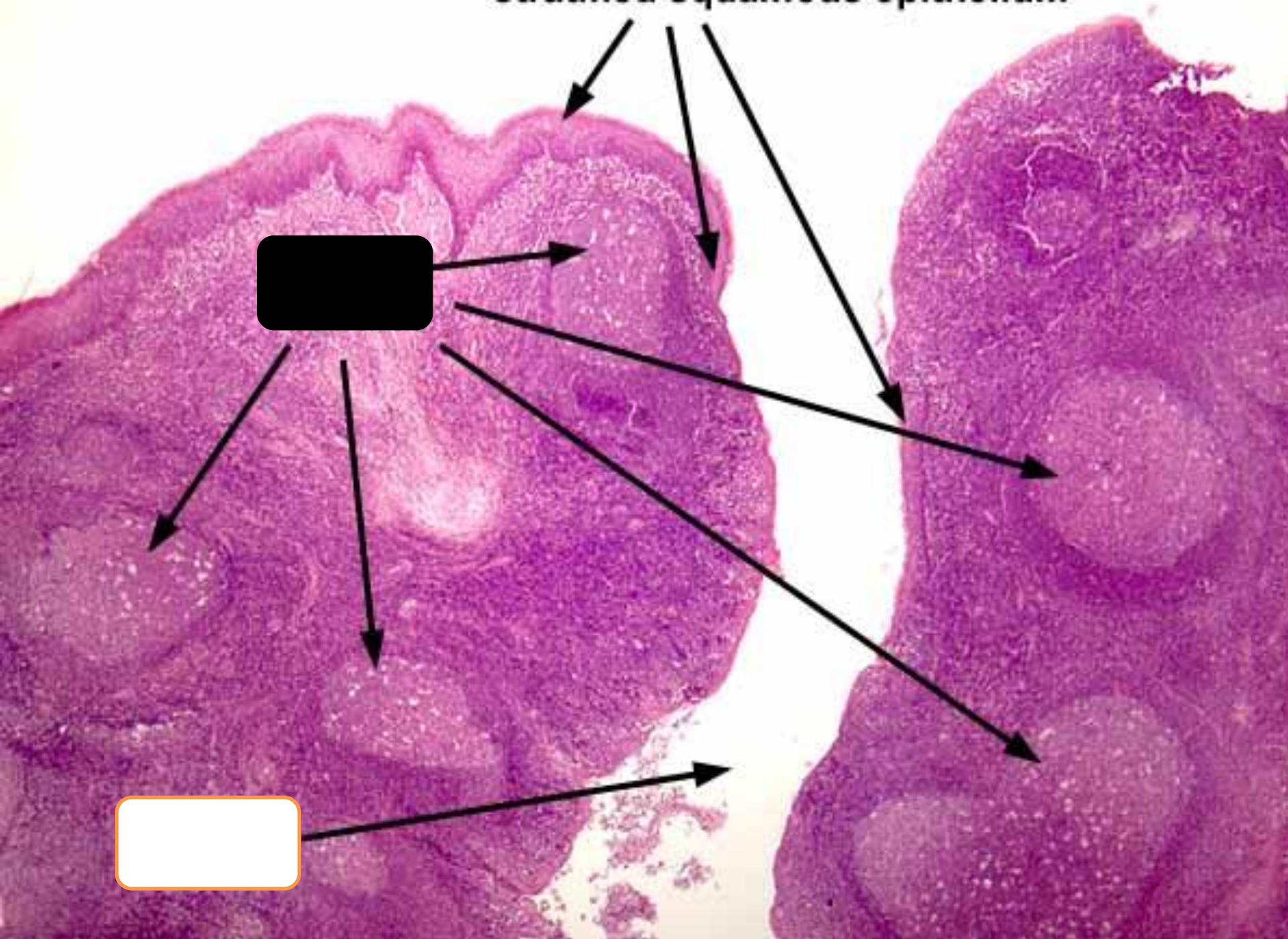


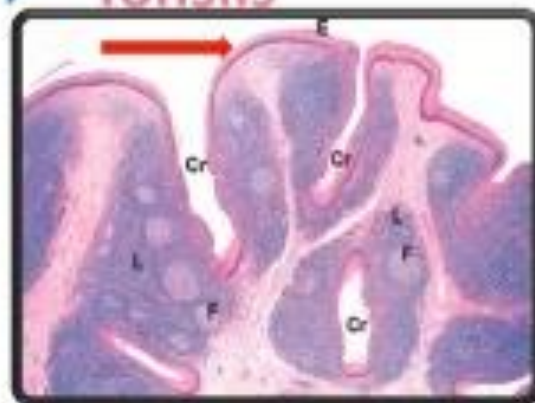
WBC pathology

Momen M. Zeineddin



★ I- Look at the covering of the tissue:

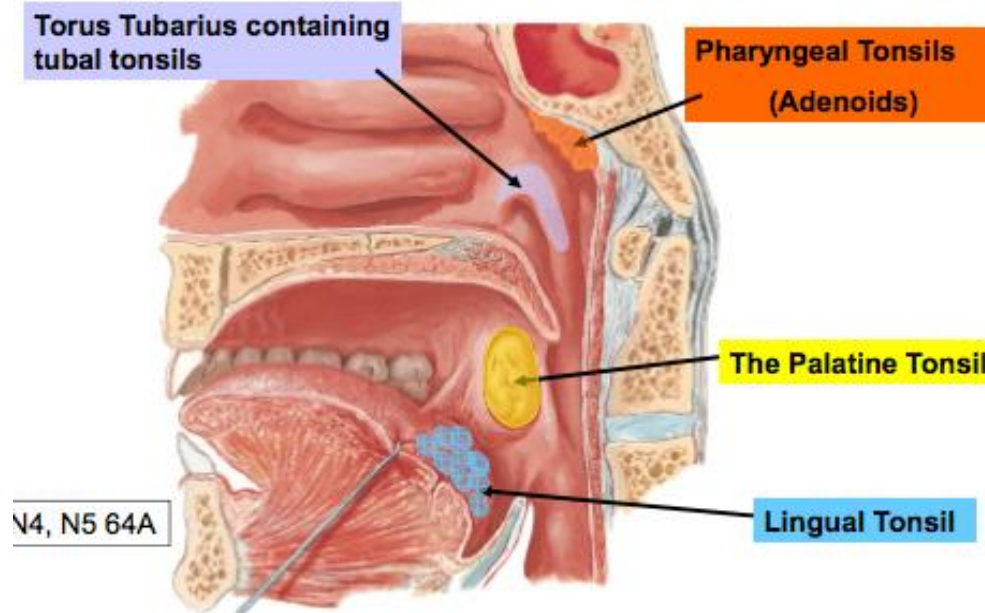
If epithelium → **Tonsils**



If CT capsule → **Thymus**
OR Lymph node
OR Spleen



Tonsillar Tissue in the Nasopharynx & Oropharynx



Palatine tonsils

Pair

In Oropharynx

Encapsulated

Stratified squamous epithelium

Adenoid (Pharyngeal tonsil)

single

Nasopharynx

Not capsulated

Mainly Pseudostratified ciliated columnar epithelium



11- Look at the distribution of lymphocytes within the tissue:

If dispersed



Thymus

If Lymphatic nodules



Lymph node

OR Spleen

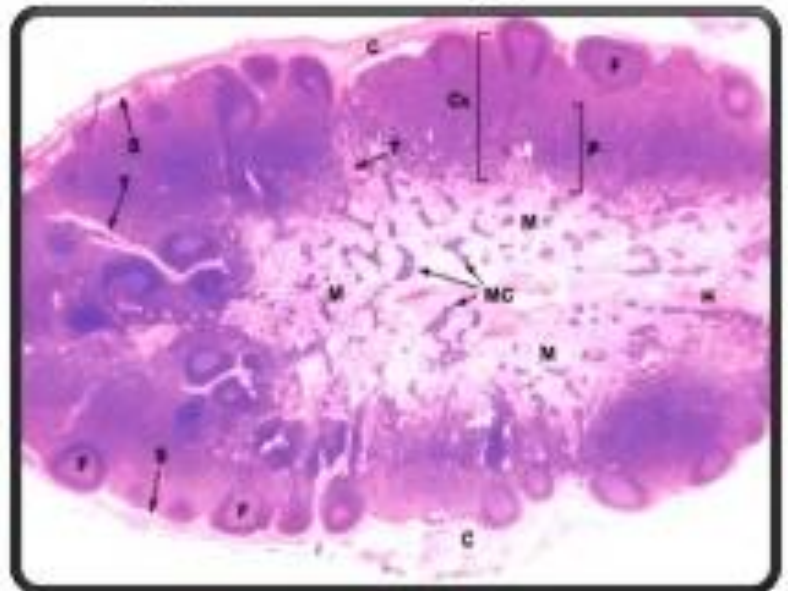


★ **III-** Look at the distribution of lymphatic nodules within the tissue during entering toward the center of the tissue:

If present under capsule only
(cortex) and disappear in the
center (medulla)

+ replaced with cords

➡ Lymph node

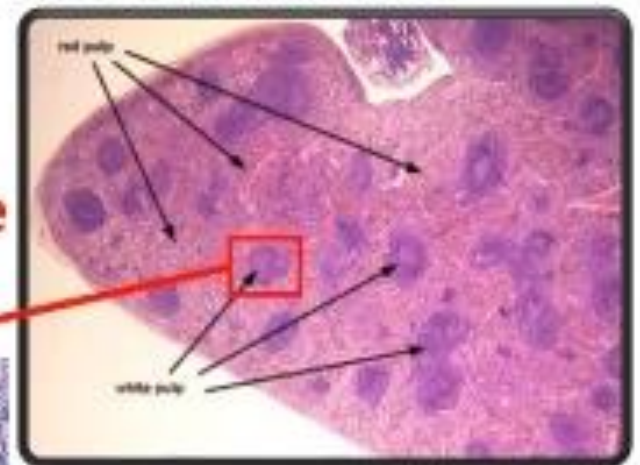
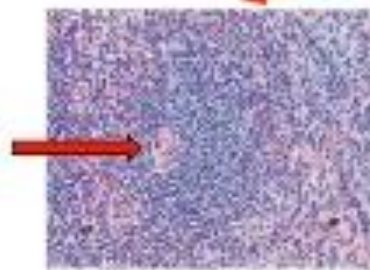


.....III- Look at the distribution of lymphatic nodules within the tissue during entering into the center of the tissue:

If present also in the center
and all over the tissue
+ presence of central artery within the
lymphatic nodules



Spleen



The thymus differ from other Lymphoid organs in the following:

1. **No** lymphatic nodules
2. **No** plasma cells.
3. **No** afferent lymphatic vessels.
4. **No** reticular fibers.
5. **Has** Hassell's corpuscles
6. **Are** concerned with maturation of T-lymphocytes.

TABLE 14-4

Important histologic comparisons of the major lymphoid organs.

	Thymus	MALT	Lymph Nodes	Spleen
Cortex/medulla	Distinctly present	Absent	Present	Absent
Lymphoid nodules	Absent	Present	Present (in cortex only)	Present (in white pulp only)
Lymphatic vessels	No afferents; few efferents in septa	No afferents; efferents present	Afferents at capsule, emptying into subcapsular sinus; efferent trabeculae at hilum	No afferents; efferents in trabeculae
Unique features	Hassall (thymic) corpuscles in medulla; epithelial- reticular cells in cortex and medulla	Crypts lined by surface mucosa in tonsils; epithelial M cells in mucosa over Peyer patches	Thin paracortical region between cortex and medulla, with high endothelial venules (HEV); medullary cords and sinuses	Minor white pulp component, with central arterioles; major red pulp component, with many sinusoids

WBC pathology

- I >> benign WBC disorders & Leukemias
- II>> Lymphomas
- III>> MPV, MDS, Histiocytic disorders.

WBC pathology

- Leukopenia:

low WBC count

**Agranulocytosis:
Severe neutropenia**

- ✓ Severe neutropenia ($ANC < 500$): significant risk for **bacterial & fungal infection**

Neutropenia causes

Decreased production.

- BM Infiltrations
- Aplastic anemia
- Chemotherapy

Increased consumption

- Immune :
Autoimmune, SLE, Drugs
- Infections
- Hypersplenism

Leukopenia

➤ Lymphopenia

➤ Causes:

- Immunodeficiency (DiGeorge syndrome or HIV)
- Whole body radiation
- Steroids , Cushing syndrome
- SLE

Severe Neutropenia

- Serious Bacterial & fungal infections
- **Agranulocytic angina:** necrotizing oral ulcer or lesions

- Management:
- Treat the cause
- Antibiotics
- GCSF



Leukocytosis

- Normal WBC: 4k-11k (5-10)
- leukocytosis : high WBC count

Causes:

- Reactive.
- Neoplastic.

Leukocytosis

- Neutrophilia : infections , Tissue necrosis, steroids
- Lymphocytosis : viral, chronic infections
- Monocytosis: Chronic infections, Connective TD, Malignancy
- Eosinophilia: Allergies, Parasites, Lymphomas
- Basophillia: CML

Leukocytosis

Neutrophilic Leukocytosis

Acute bacterial infections (especially those caused by pyogenic organisms); sterile inflammation caused by, e.g., tissue necrosis (myocardial infarction, burns)

Eosinophilic Leukocytosis (Eosinophilia)

Allergic disorders such as asthma, hay fever, allergic skin diseases (e.g., pemphigus, dermatitis herpetiformis); parasitic infestations; drug reactions; certain malignancies (e.g., Hodgkin lymphoma and some non-Hodgkin lymphomas); collagen-vascular disorders and some vasculitides; atheroembolic disease (transient)

Basophilic Leukocytosis (Basophilia)

Rare, often indicative of a myeloproliferative neoplasm (e.g., chronic myeloid leukemia)

Monocytosis

Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis, and malaria; collagen vascular diseases (e.g., systemic lupus erythematosus); and inflammatory bowel diseases (e.g., ulcerative colitis)

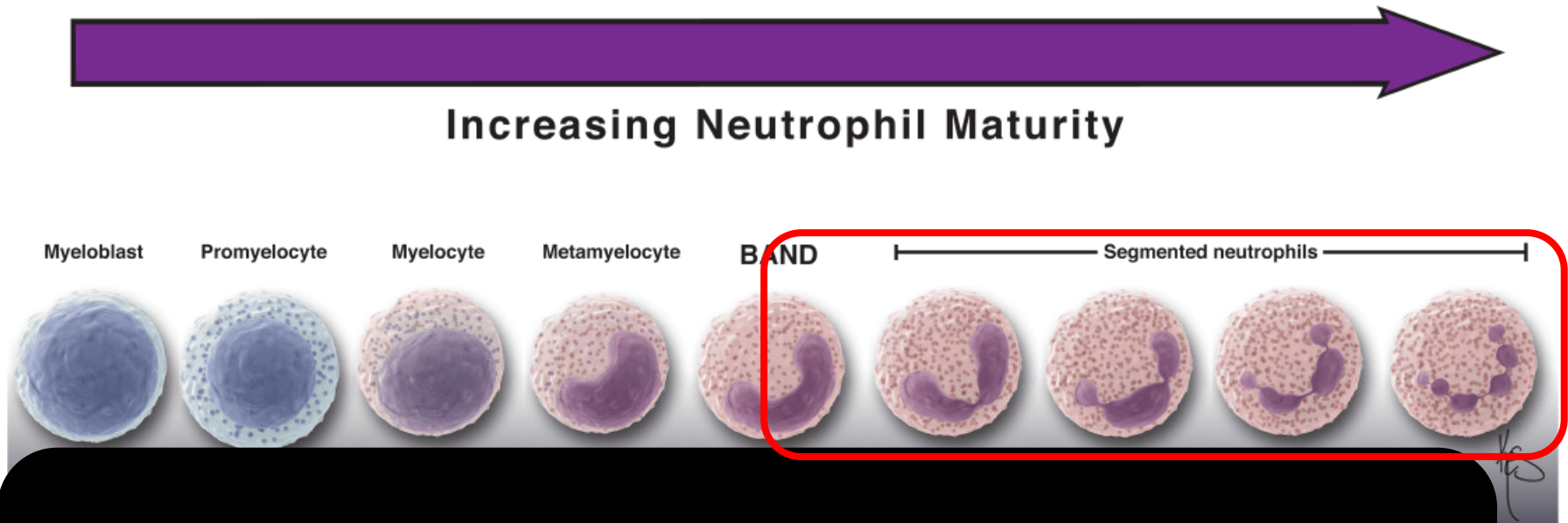
Lymphocytosis

Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis); viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); *Bordetella pertussis* infection

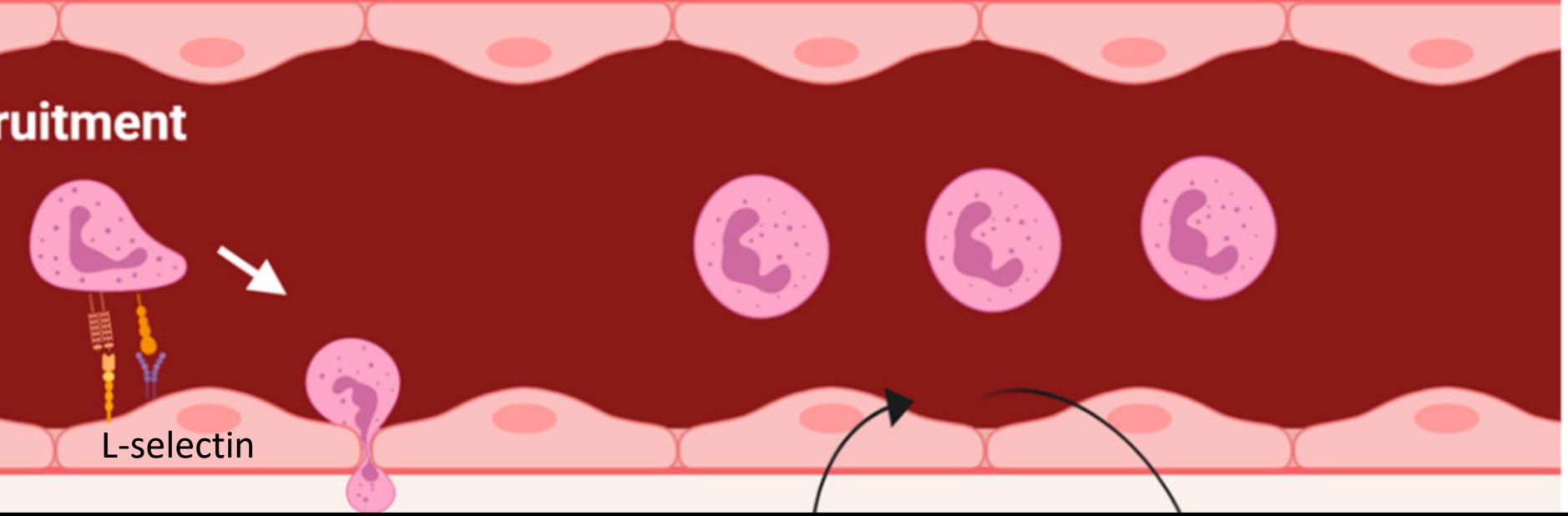
Neutrophilia

- **Neutrophilia:** increased circulating neutrophils
- **Causes :**
 - Bacterial infection
 - Tissue necrosis: MI, burns
 - Steroids
- **Mechanisms:**
 - Left shift: increase in the number of immature cell types among the blood cells
 - Demargination
 - Slower migration

ELEVATED BAND COUNT - “LEFT SHIFT”



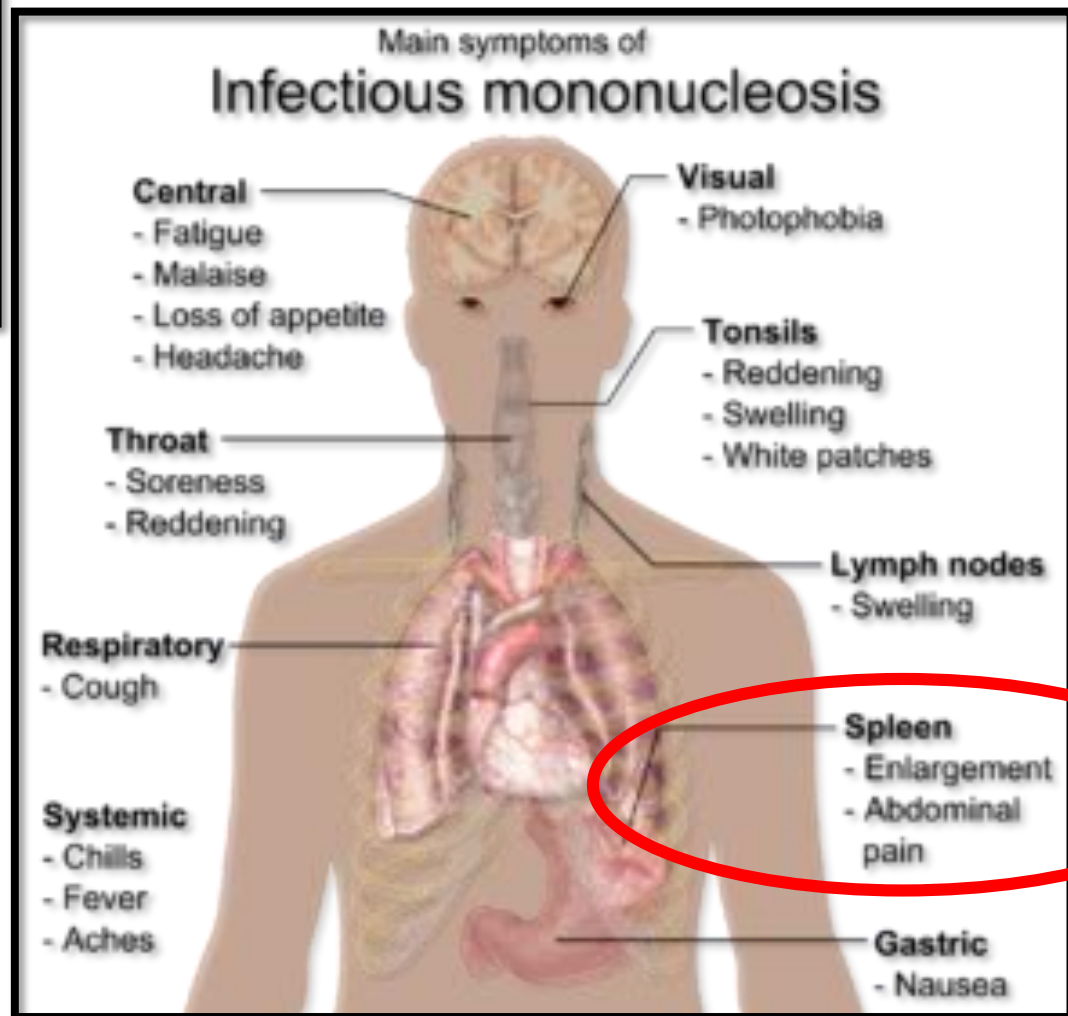
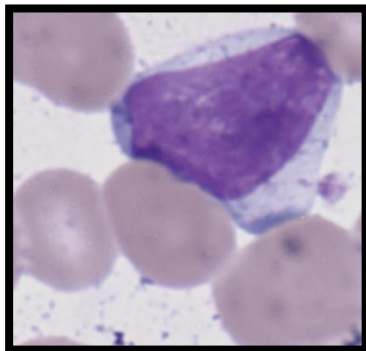
- **Left shift: increase in the number of immature cell types among the blood cells**
- **leukemoid reaction (vs leukemia):**
increased WBC ($> 50,000$ cells/ μL), which is a physiological response to stress or infection



- Demargination: Within minutes of exercise, surgery, or stress, one can see an increased number of circulating neutrophils
- Slower migration (Steroids): affects neutrophils migration to peripheral tissues

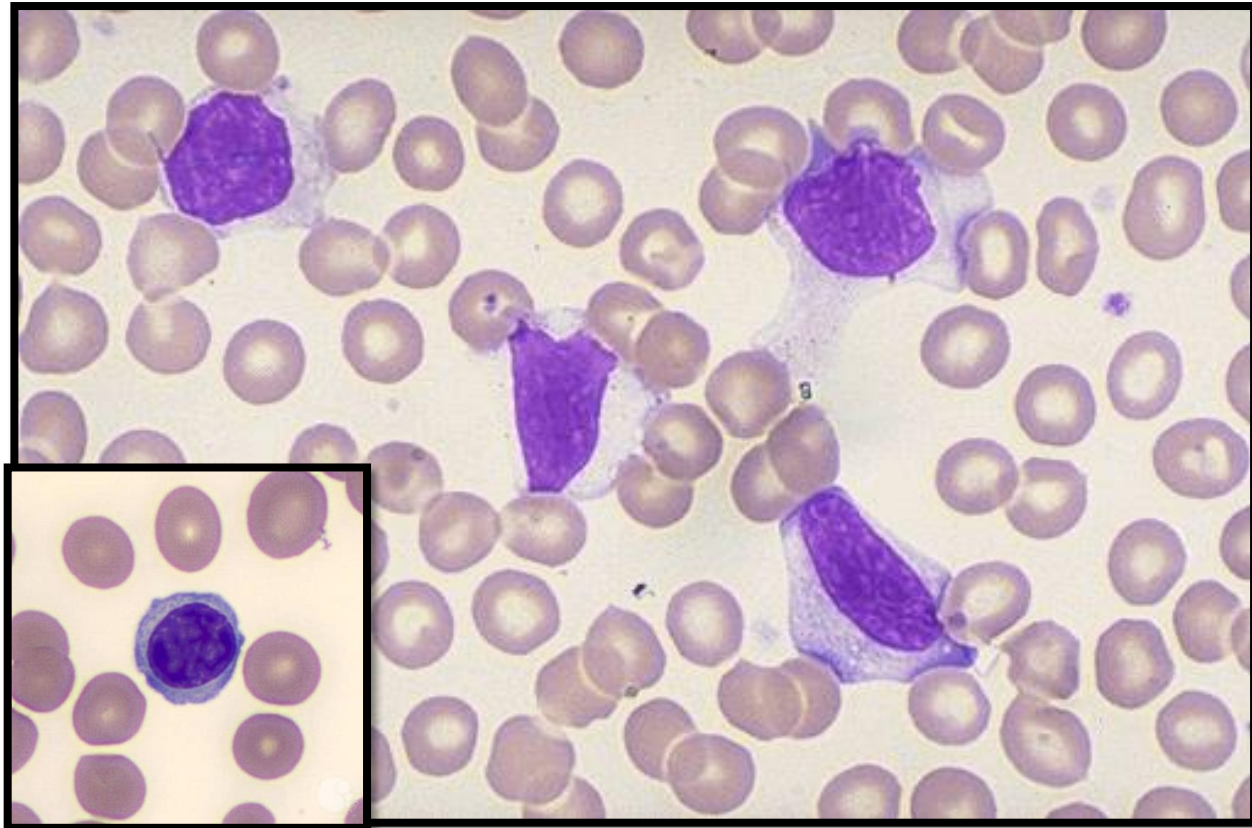
Infectious Mononucleosis

- Acute, self-limited disease
 - EBV, herpes virus
 - Direct oral contact "kissing disease"
 - Indirect utensils, cups, spoon
 - Young adults
-
- CMV may induce a similar syndrome



Infectious Mononucleosis

- Leukocytosis (Lymphocytosis)
- Atypical lymphocytes (larger cells, abundant cytoplasm, oval folded nucleus)(CD8+ T cells)



Infectious Mononucleosis

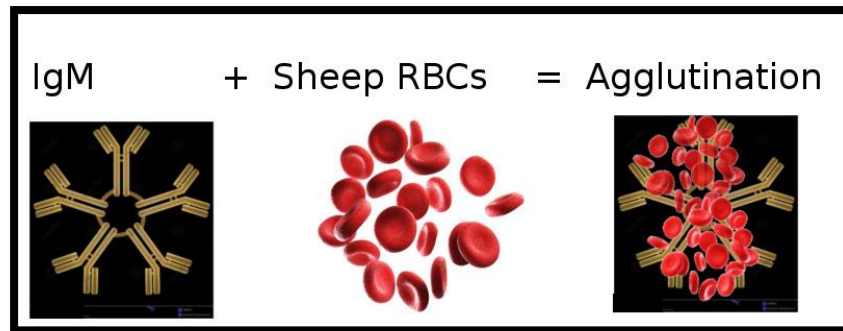
CD8+ T-cell response leads to:

- Atypical lymphocytosis
- Generalized lymphadenopathy (Paracortical hyperplasia)
- Splenomegaly due to T-cell hyperplasia in the PALS

Infectious Mononucleosis

Monospot test (IM Heterophile test):

EBV IgM cross-react with horse or sheep RBCs



- A negative monospot test suggests CMV or early testing in the 1st wk

Infectious Mononucleosis

➤ **Complications:**

- Splenic rupture
- Ampicillin rash
- Dormancy of EBV in B cells >> B-cell lymphoma

Reactive lymphadenitis

**Acute nonspecific
lymphadenitis**

- Localized
- Genaralized

**Chronic non specific
Lymphadenitis**

Swollen Lymph Nodes



Normal Lymph Node



Abnormal Lymph Nodes

FIGURE 14-15 Lymph node.

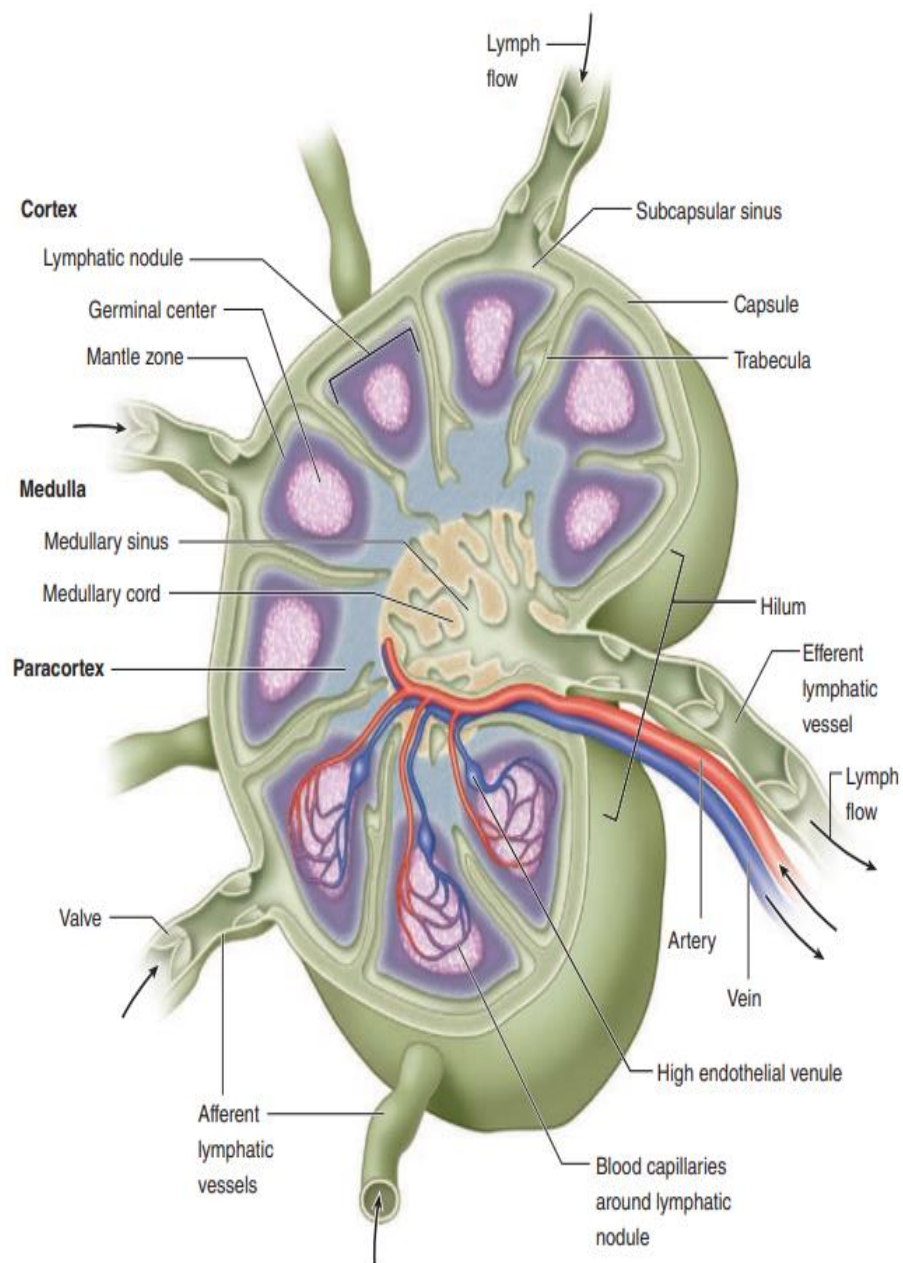
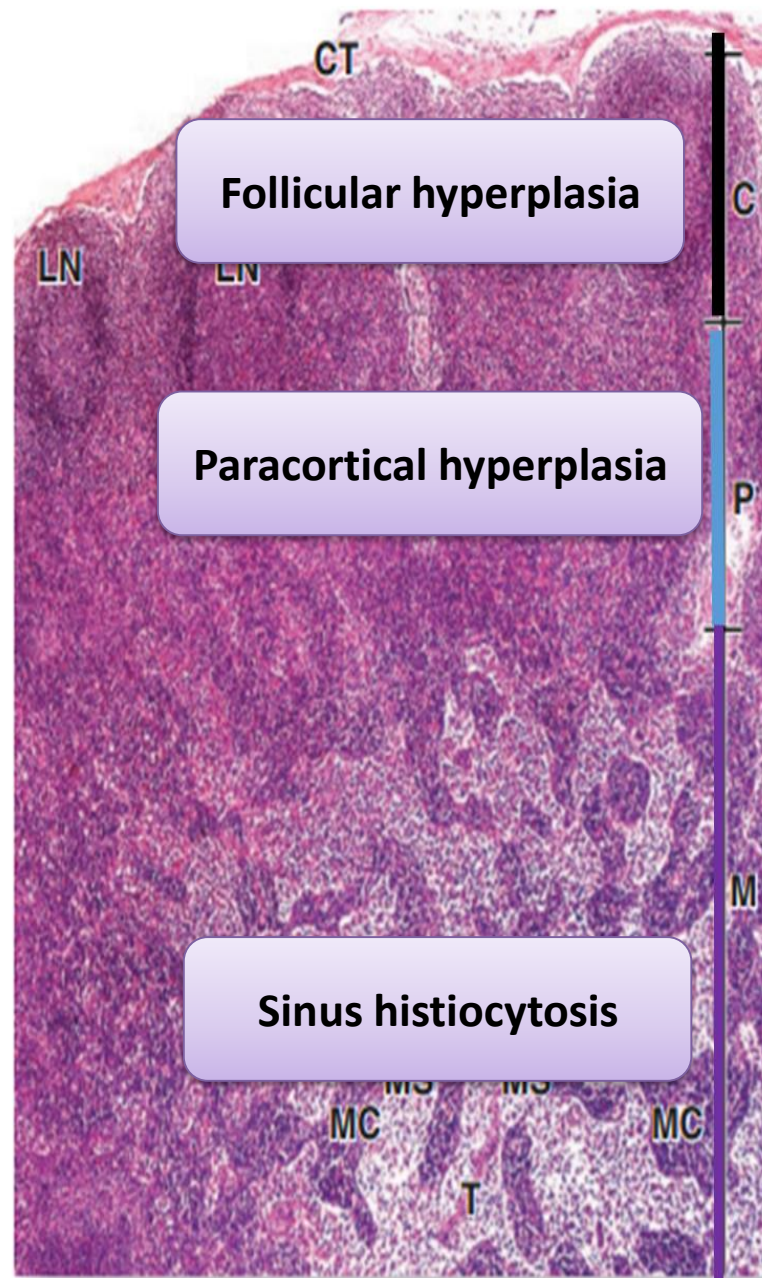


FIGURE 14-16 Regions of a lymph node.



Follicular hyperplasia

- Follicular (germinal center)
- RA, Early HIV

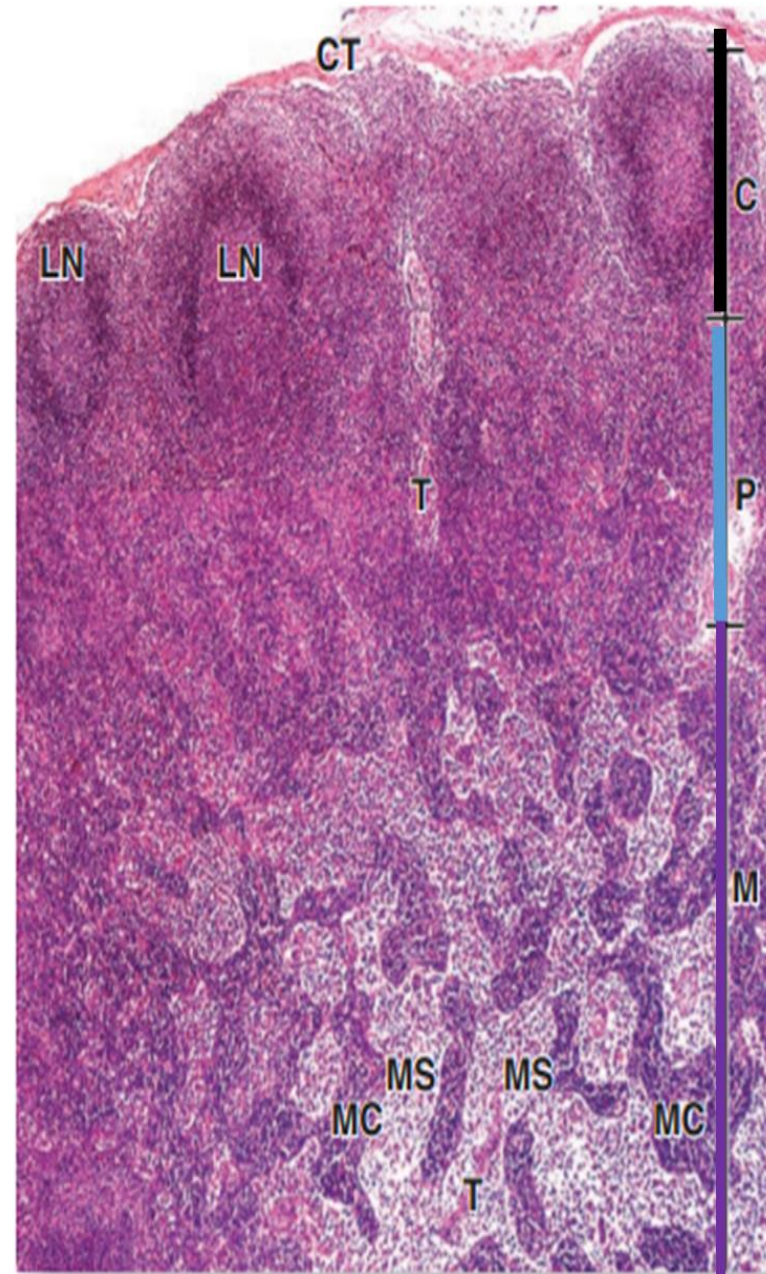
Paracortical hyperplasia

- T cell
- EBV, Drug reaction

Sinus histiocytosis

- Distention of lymphatic sinusoids
- Cancers

FIGURE 14–16 Regions of a lymph node.



Reactive lymphadenitis

**Acute nonspecific
lymphadenitis**

**Localized
Generalized**

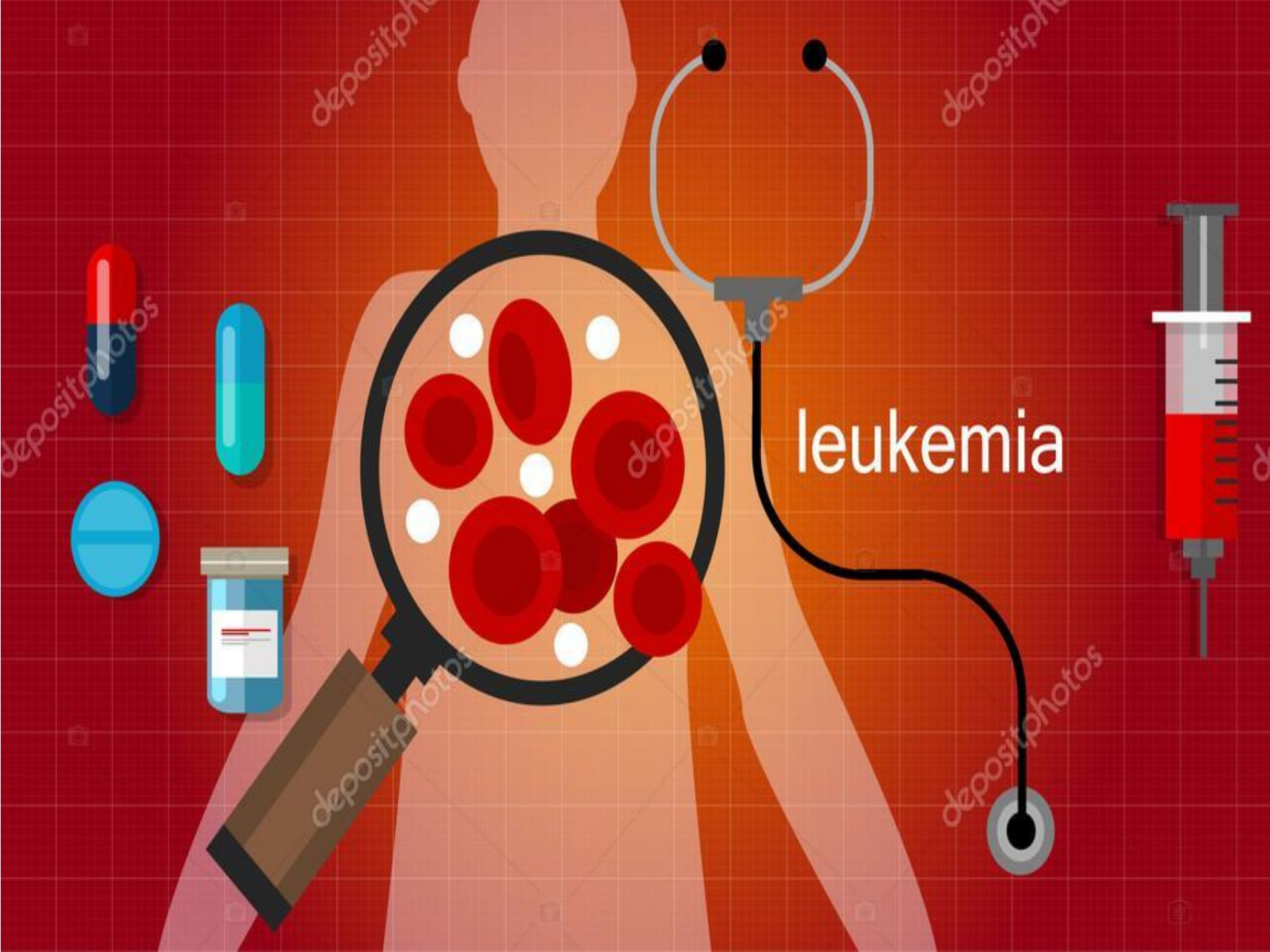
**Chronic non specific
Lymphadenitis**

Follicular hyperplasia

Paracortical hyperplasia

Sinus histiocytosis

leukemia

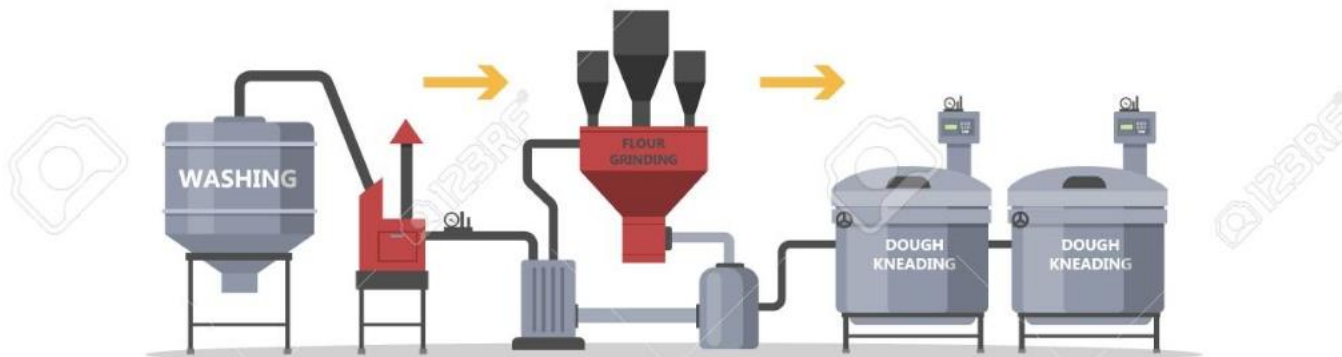


Leukemias

- BM cancer
- Neoplastic proliferations -mostly- of WBC precursors

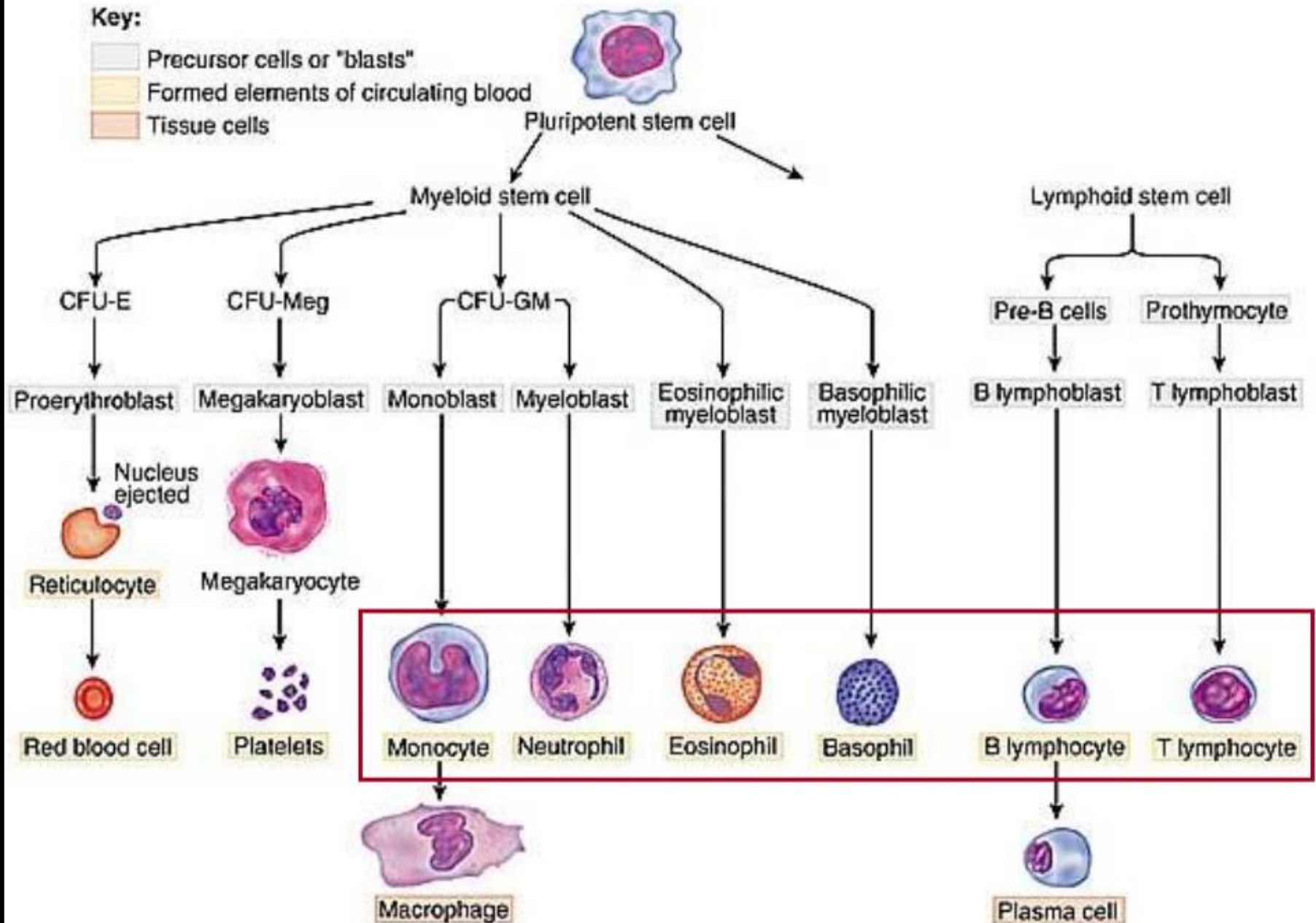
Acute vs Chronic leukemia

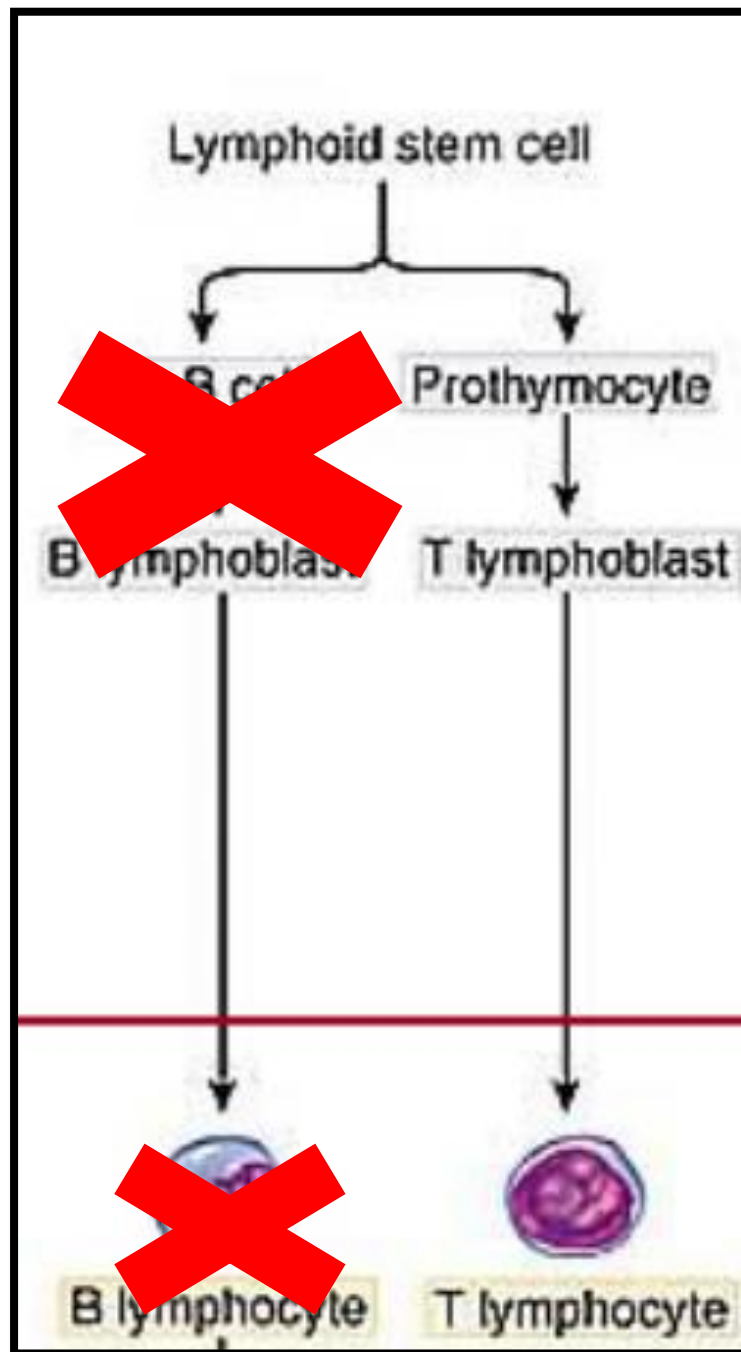
	Acute leukemia	Chronic leukemia
Presentation	Days to weeks	Months..
Course		
Leukemic cells		
Maturation arrest		



Key:

-  Precursor cells or "blasts"
-  Formed elements of circulating blood
-  Tissue cells





Acute vs Chronic leukemia

	Acute leukemia	Chronic leukemia
Presentation	Days to weeks	Months..
Course	Rapidly fatal if not treated	Survive for years
Leukemic cells		
Maturation arrest		

Leukemias

- ALL
- AML
- CLL
- CML

ACUTE LEUKEMIA

- Neoplastic proliferation of **blasts**; characterized by accumulation of **> 20% blasts** in the bone marrow
- ALL vs AML

Etiology

- ❑ Unknown

- ❑ Risk factors

- **Genetic RF:** -Down synd
-Fanconi anemia

- **Environmental**

- Viruses : Human t-Lymphotropic virus

- Adult T-leukemia

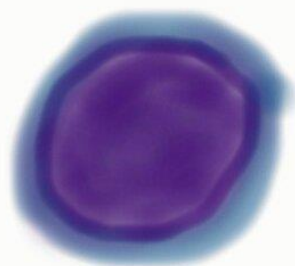
- EBV >> Burkitt

- Radiation

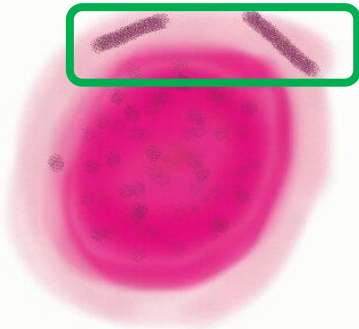
- Chemotherapy, benzene

ALL

AML



Lymphoblast



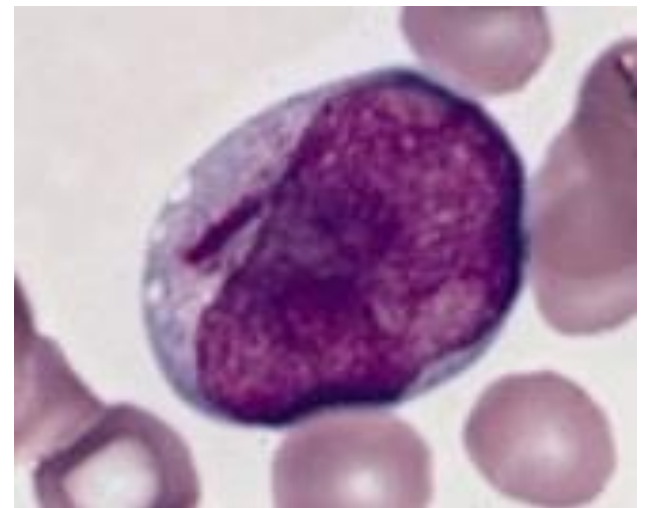
Myeloblast

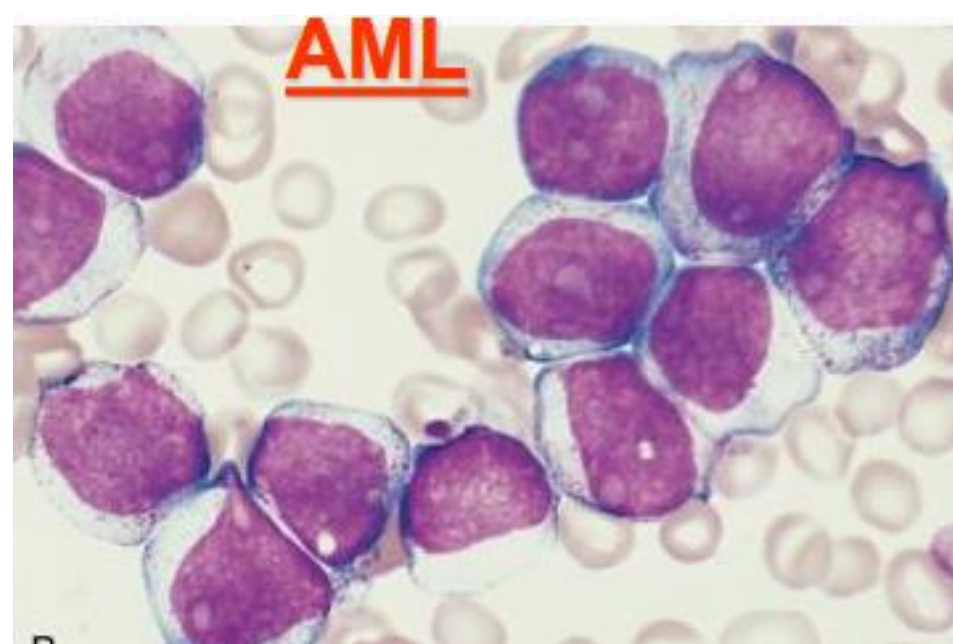
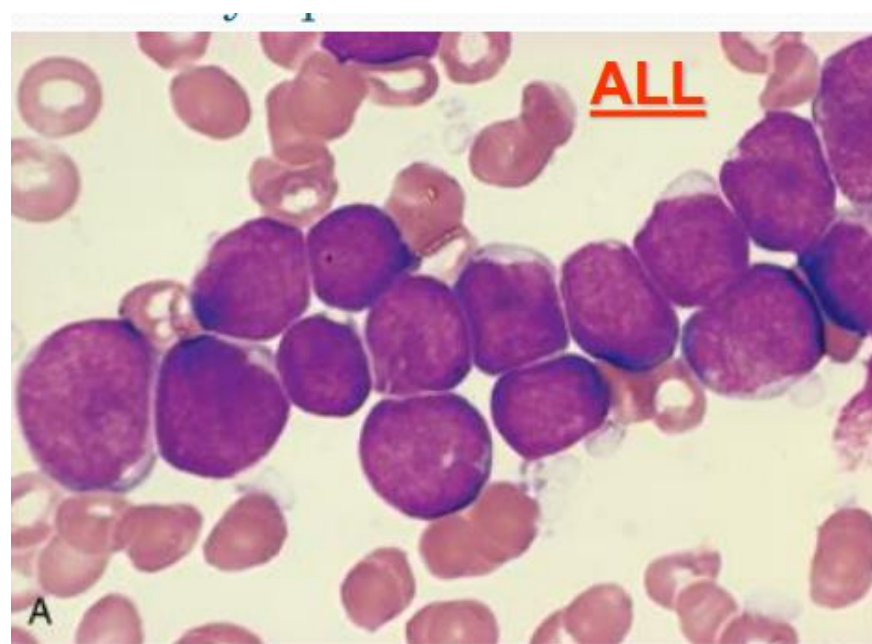
- Clumped chromatin
- High NC ratio
- 1,2 nucleoli
- **TdT +ve**
- MPO -ve

- Larger
- Delicate chromatin
- Abundant cytoplasm
- Many nucleoluses
- **MPO +ve, TdT -ve**

Auer rods

- **Auer rods** are large cytoplasmic inclusion bodies in the myeloblast.
- Fused lysosomal remnants.
- AML especially AML-M3

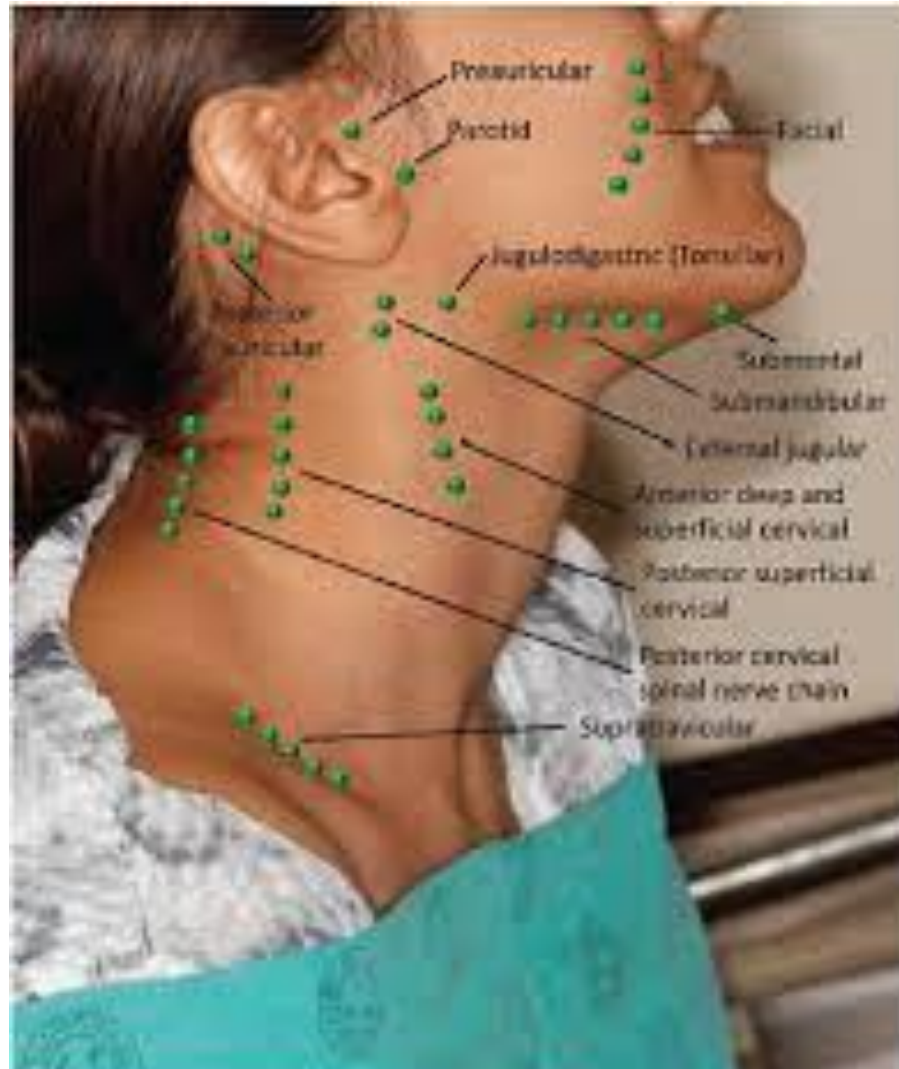




Clinically

- Fever, hypoactivity, sweats, Bony pains
- BM: anemia symptoms, Infections, bleedings
- HSM
- CNS: headache, vomiting, CN palsies

ALL >> lymphadenopathy



T-ALL>> Thymic enlargement



Source: K. Kaushansky, M.A. Lichtman, J.T. Prchal, M.M. Levi, O.W. Press, L.J. Burns,
M. Caligiuri: Williams Hematology, 9th edition
www.accessmedicine.com
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AML>>Gum hypertrophy



	Acute leukemia	Chronic leukemia
Presentation	Days to weeks	months
Course	Rapidly fatal if not treated	Survive for years
Leukemic cells	Undifferentiated/blasts	differentiated
Maturation arrest	BM failure	No failure

ALL

- **Commonest childhood cancer**
- Peak **2-5 Y/O**
- Neoplastic accumulation of **lymphoblasts** (> 20%)
in the bone marrow
- Elevated WBC , NL WBC, **aleukemic leukemia**
- **Pancytopenia**

Types

❖ **B-ALL** : The most common type of ALL
B-lymphoblasts (TdT +)
CD10, CD19, and CD20

❖ **T-ALL** :
T-lymphoblasts (TdT +)
CD2, CD3, CD4, CD7, CD8

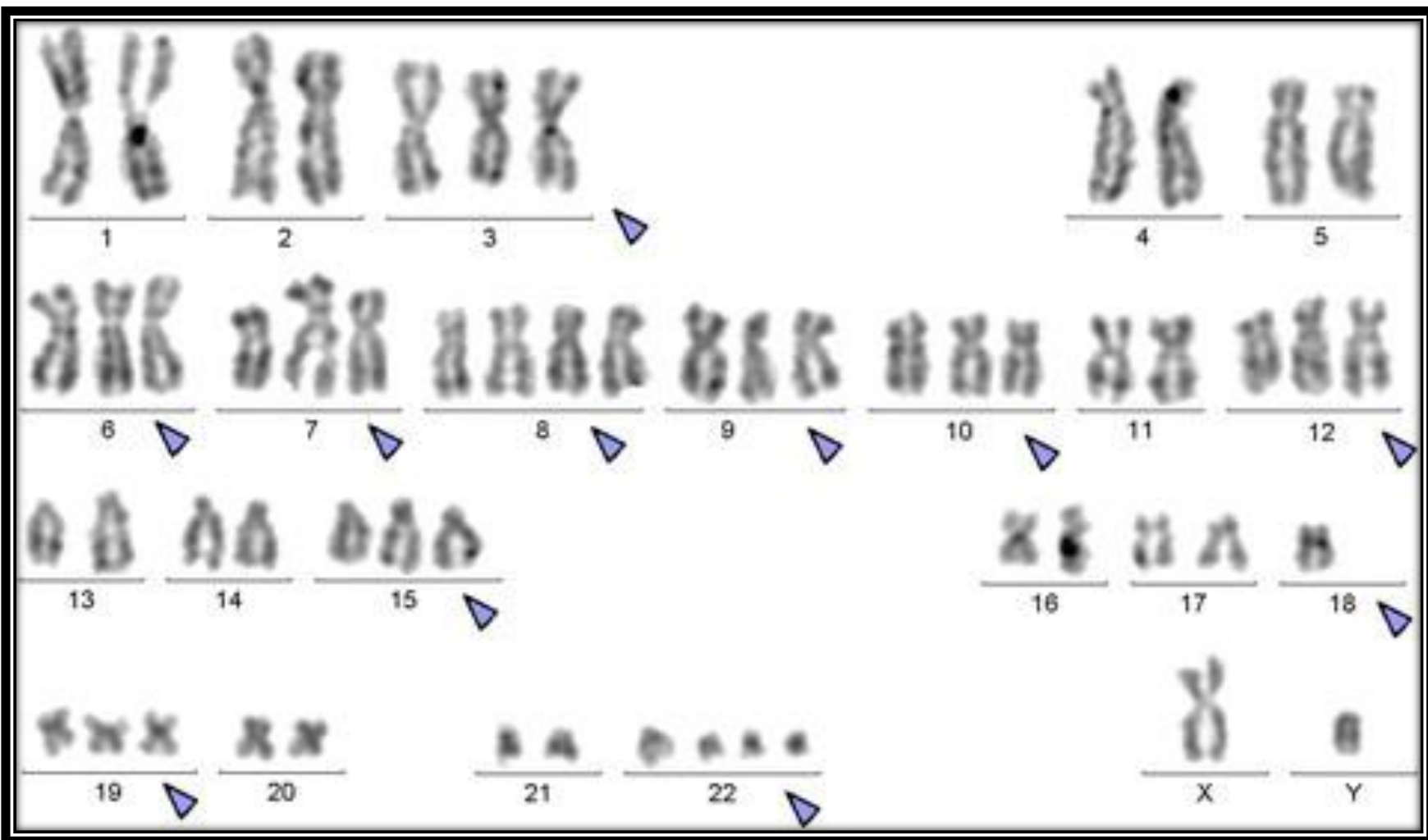
Prognostic factors

Good prog factors

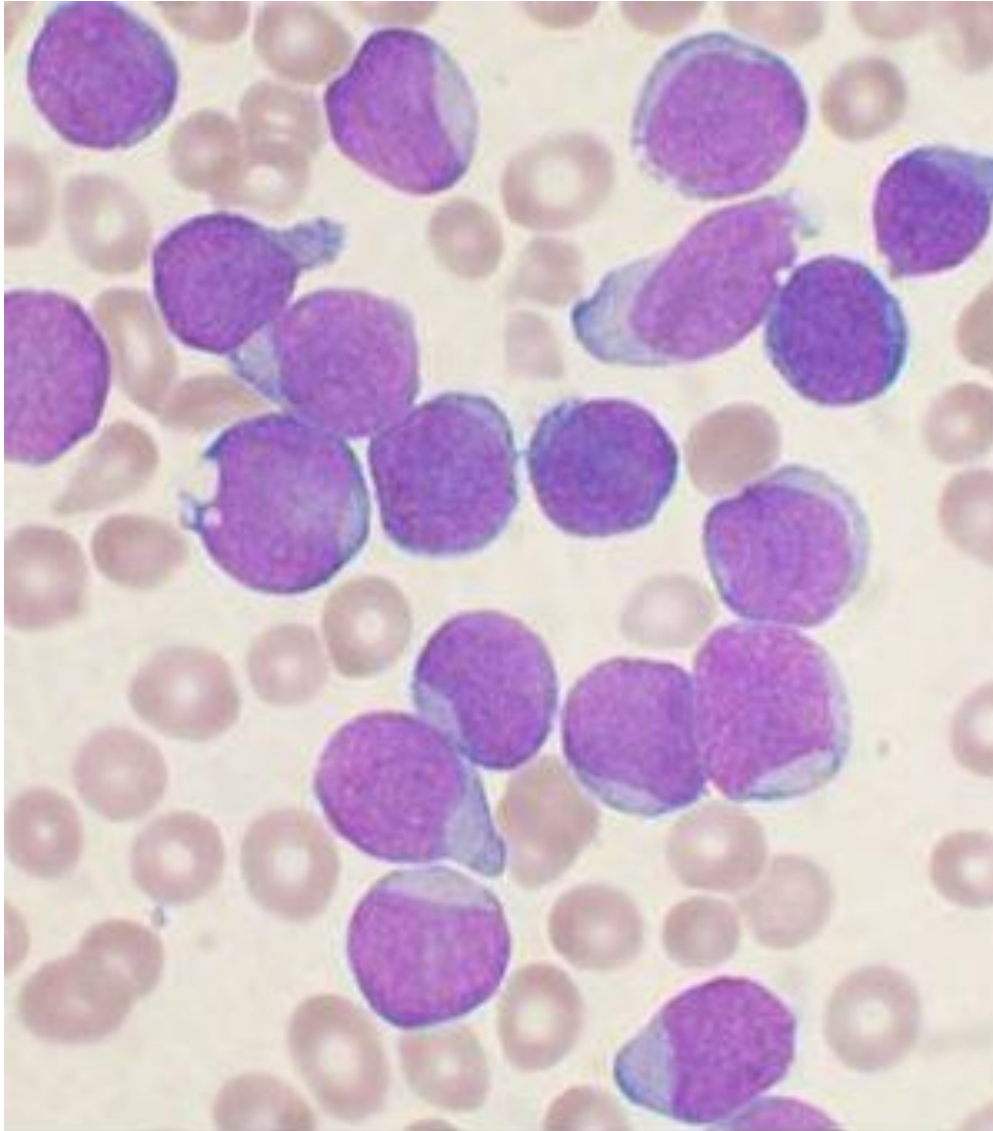
- Age 1-10
- WBC < 50k
- CNS -ve
- B-ALL (CD10 +ve)
- Hyperdiploidy
- t(12,21)

Bad prog factors

- Infants, adolescents
- WBC > 50k
- CNS +ve
- T-ALL
- Hypoploidy
- T (9,22) philidaliphia ch



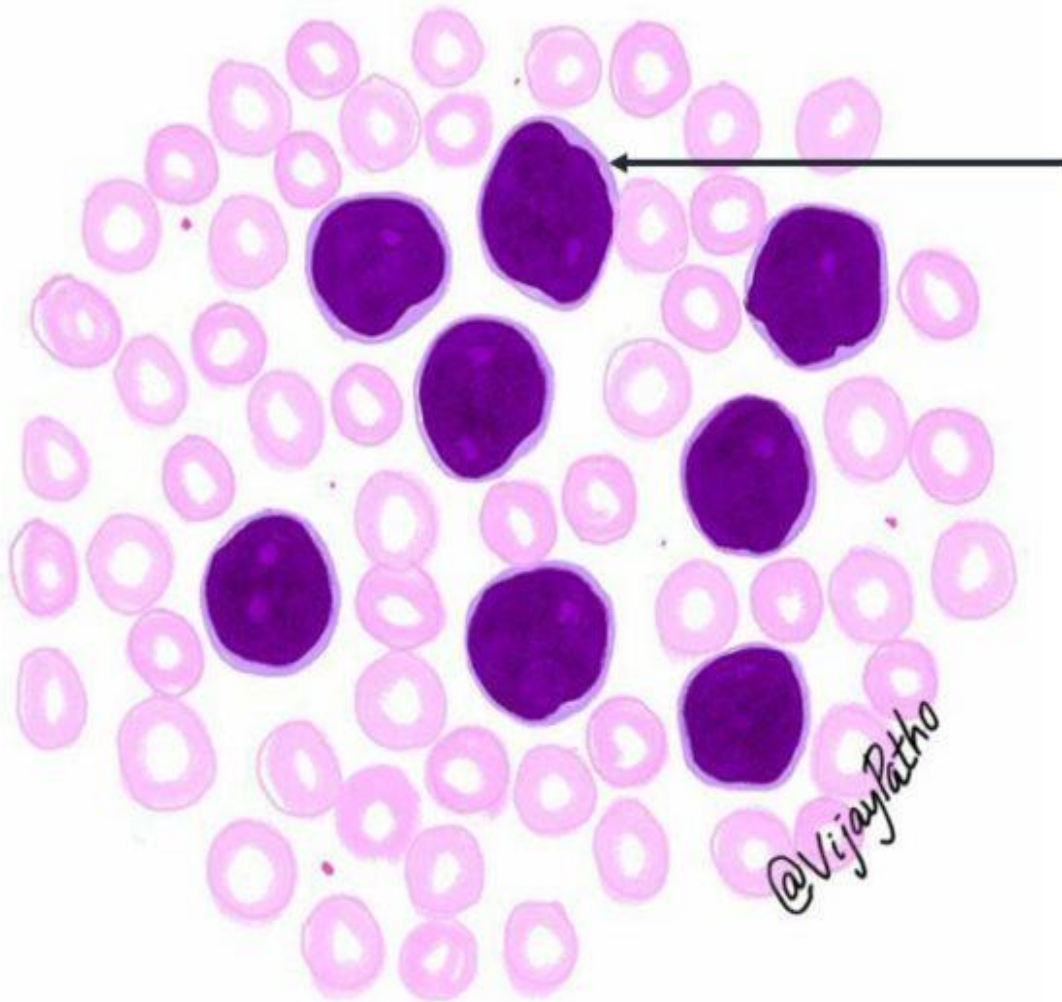
Blood smear



ALL-Bone Marrow

- Increased Bone marrow cellularity
- Blast cells at least 20%

ACUTE LYMPHOBLASTIC LEUKEMIA



Large cell with round to oval nucleus, with coarse, clumped chromatin, and inconspicuous nucleoli and scanty cytoplasm

LYMPHOBLAST

@VijayPatho
@VijayPatho

FAB Classification

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



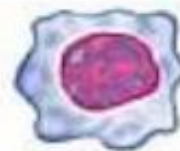
Large, homogeneous cell population. Nuclei regular with fine chromatin and 1-2 nucleoli. Moderate to abundant vacuolated cytoplasm

Key:

 Precursor cells or "blasts"

 Formed elements of circulating blood

 Tissue cells



Pluripotent stem cell

Myeloid stem cell

CFU-E

CFU-Meg

CFU-GM

Proerythroblast

Megakaryoblast

Monoblast

Myeloblast

Eosinophilic
myeloblast

Basophilic
myeloblast

Nucleus
ejected

Reticulocyte

Megakaryocyte

Red blood cell

Platelets

Monocyte

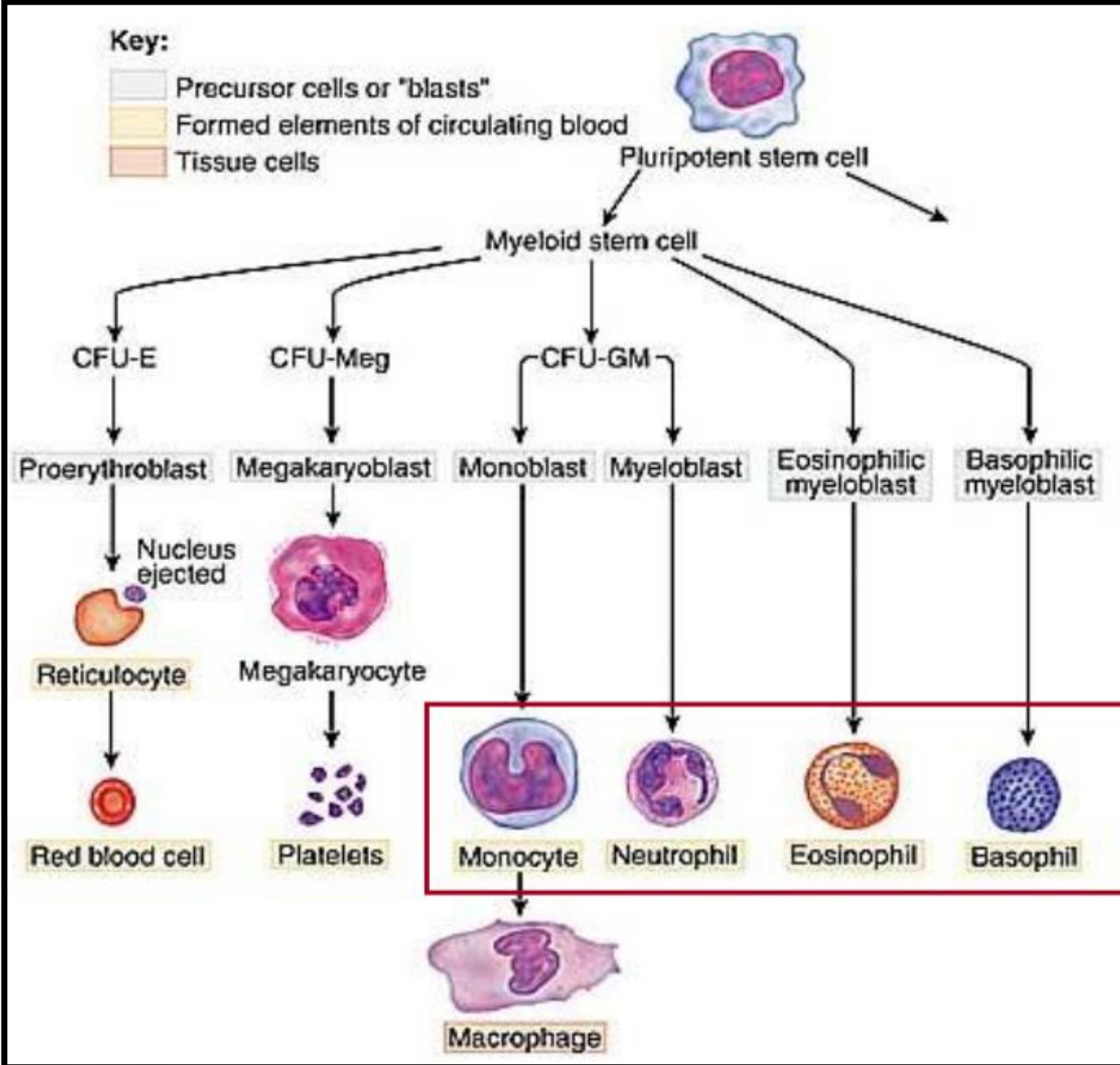
Neutrophil

Eosinophil

Basophil



Macrophage



AML

- Neoplastic accumulation of immature myeloid cells (**myeloblasts**) (> 20%) in the bone marrow
- Myeloblasts :MPO +ve
- Primarily affects **adults**
- Incidence increases with age
- **MDS** is predisposing factor

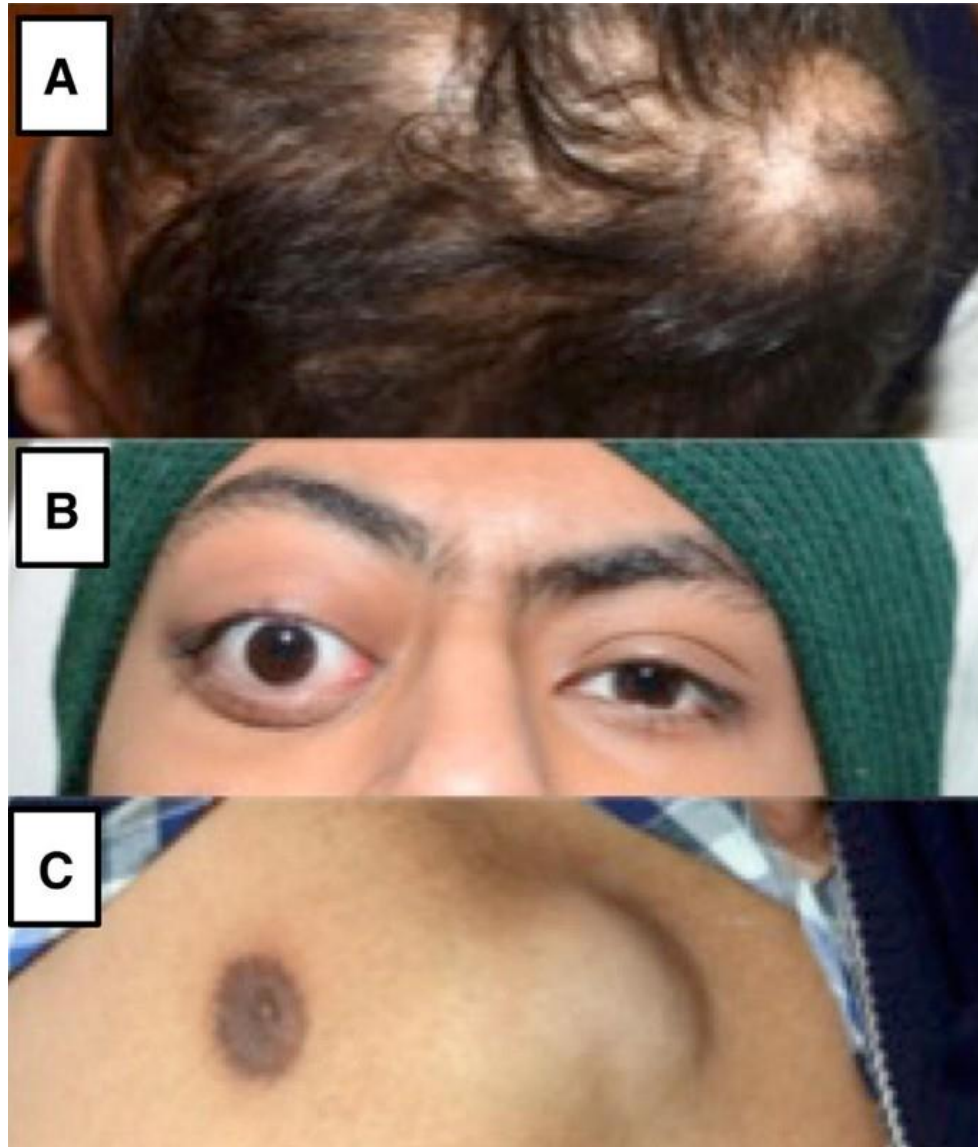
Clinically

- Fever, hypoactivity, sweats, Bony pains
- **BM**: anemia symptoms, Infections, bleedings
- HSM, usually **no lymphadenopathy**
- CNS: headache, vomiting CN palsies
- Chloromas, **myeloid sarcoma**

AML>>Gum hypertrophy



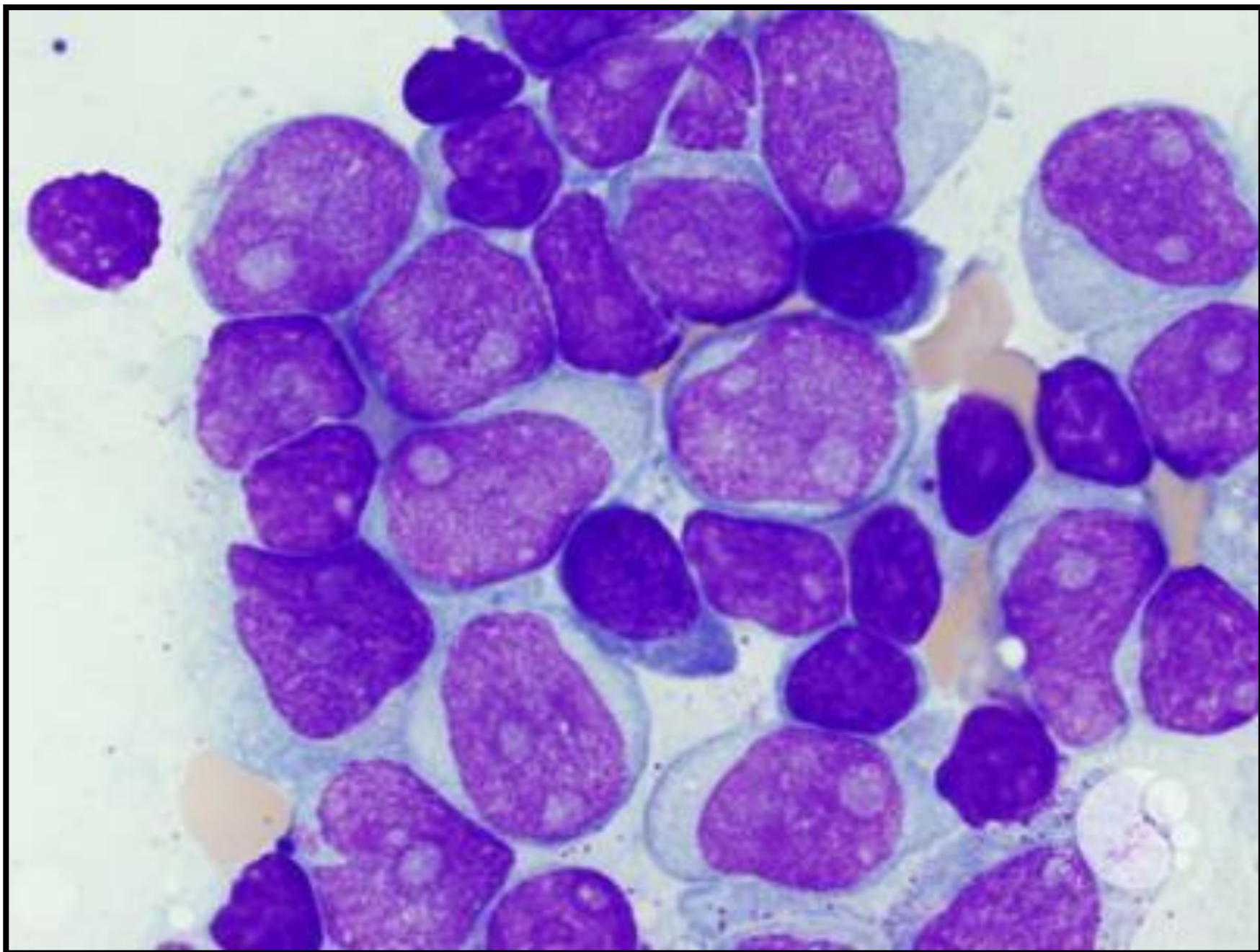
AML-Chloroma



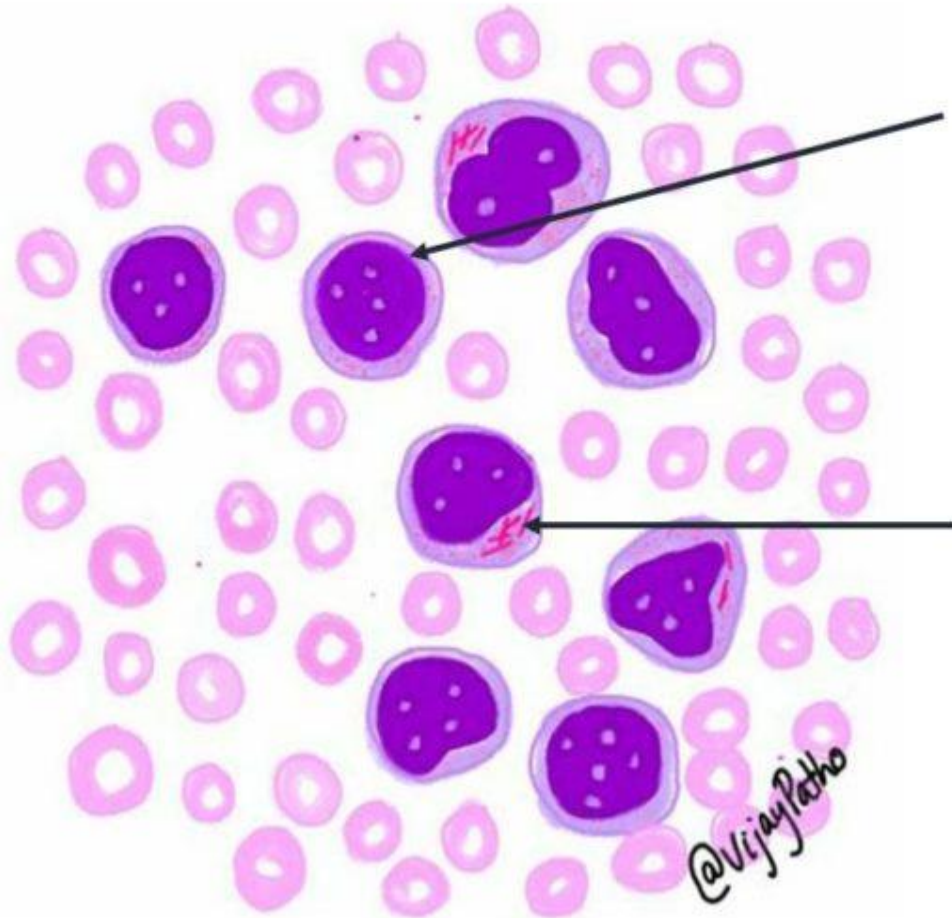
AML

FAB Classification of AML

- M0 undifferentiated acute myeloblastic leukemia (5%)
- M1 AML with minimal maturation (20%)
- M2 AML with maturation (30%)
 - t(8;21)
- M3 Acute promyelocytic leukemia (5%)
 - t(15;17)
- M4 Acute myelomonocytic leukemia (20%)
- M4 eos Acute myelomonocytic leukemia with eosinophilia (5%)
 - inv (16)
- M5 Acute monocytic leukemia (10%)
 - t(9;11)
- M6 Acute erythroid leukemia (3%)
- M7 Acute megakaryoblastic leukemia (3%)



ACUTE MYELOBLASTIC LEUKEMIA



Large cell with round to oval nucleus, with fine chromatin, and 2 to 4 nucleoli and scanty cytoplasm with fine granules

MYELOBLAST

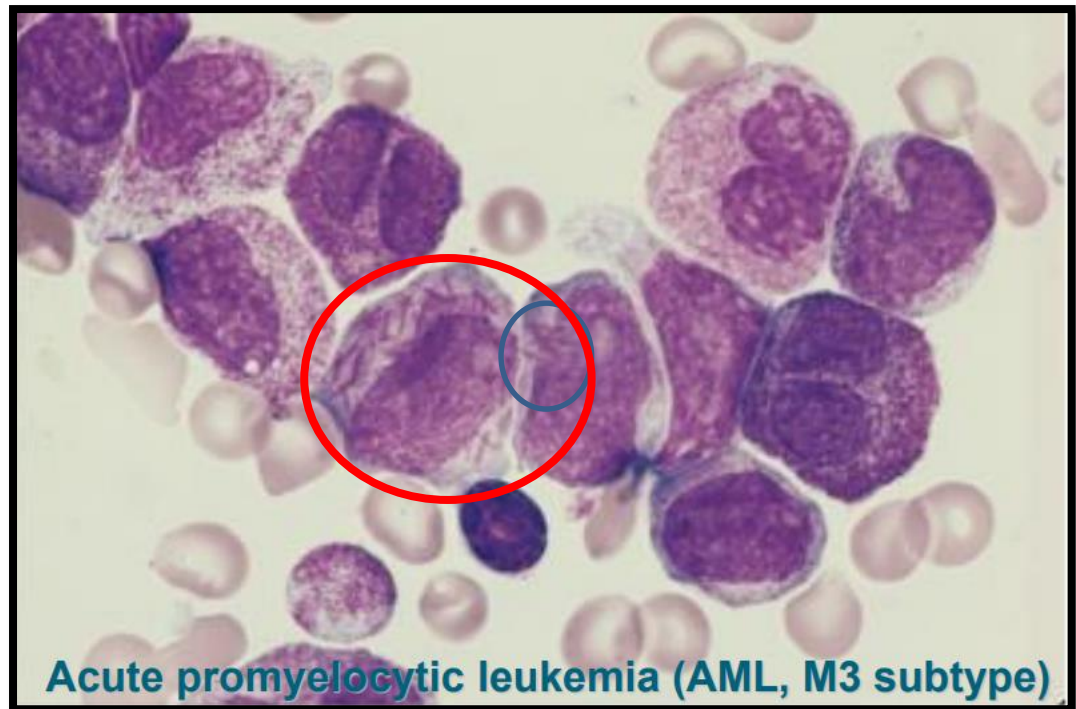
Crystalline cytoplasmic inclusions as a result of abnormal fusion of azurophilic granules

AUER RODS

@VijayPatho

AML M3

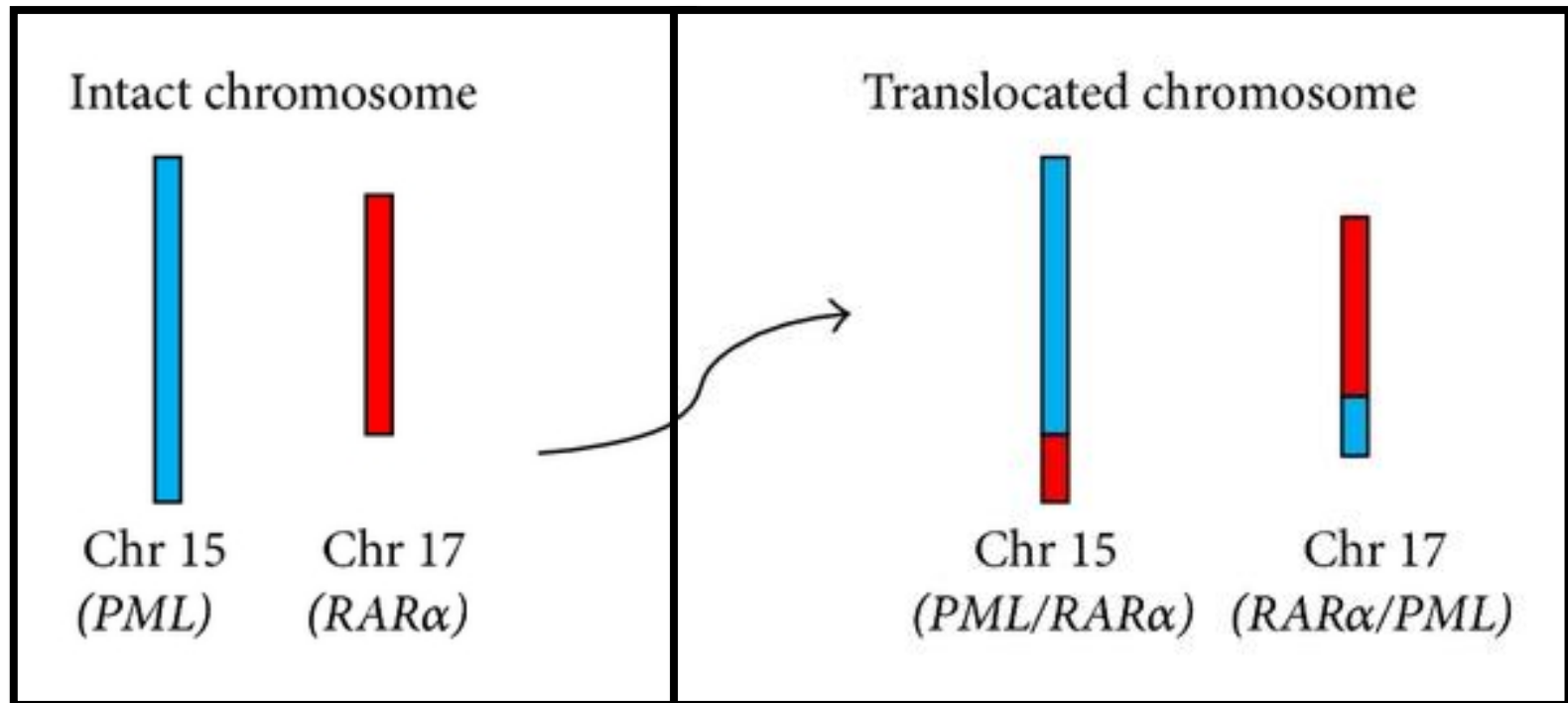
- **Acute Promyleocytic leukemia**
- BMA: neoplastic **promyelocytes** with abnormally coarse azurophilic granules.
- Auer rods
- Faggot cell



Retinoic Acid Receptor A

Promyelocytic leukemia

abnormal fusion gene sequence.



AML-M3

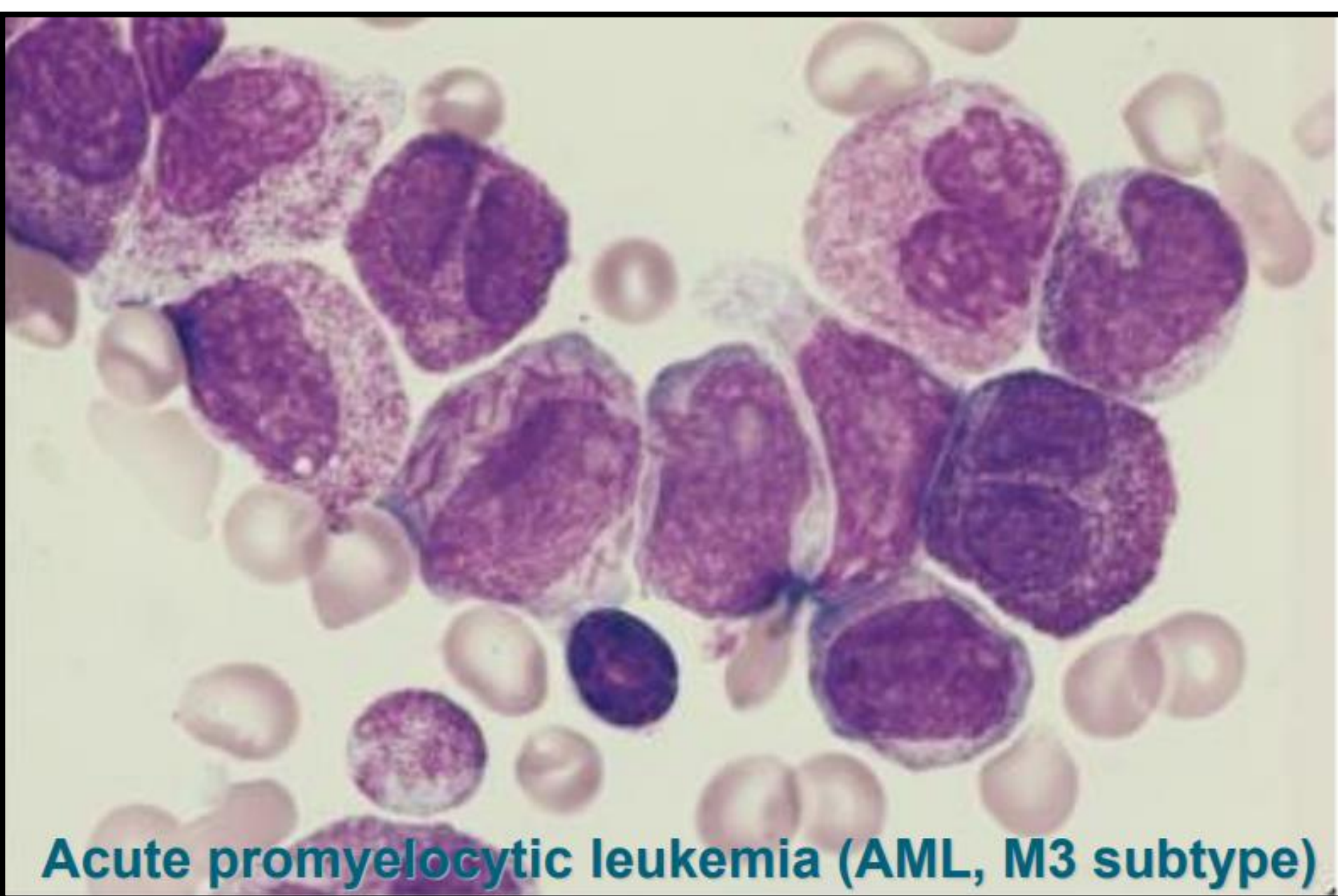
Acute promyelocytic leukemia (APL)

- **t(15;17)- PML _RARA**
- Leads to **block promyelocytes maturation** and to promyelocytes (blasts) accumulation.
- Abnormal **promyelocytes** contain numerous primary granules that increase the risk for **DIC**.

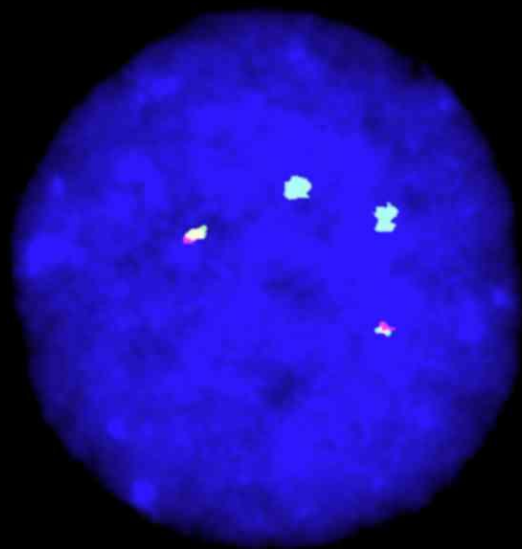
AML-M3

Acute promyelocytic leukemia (APL)

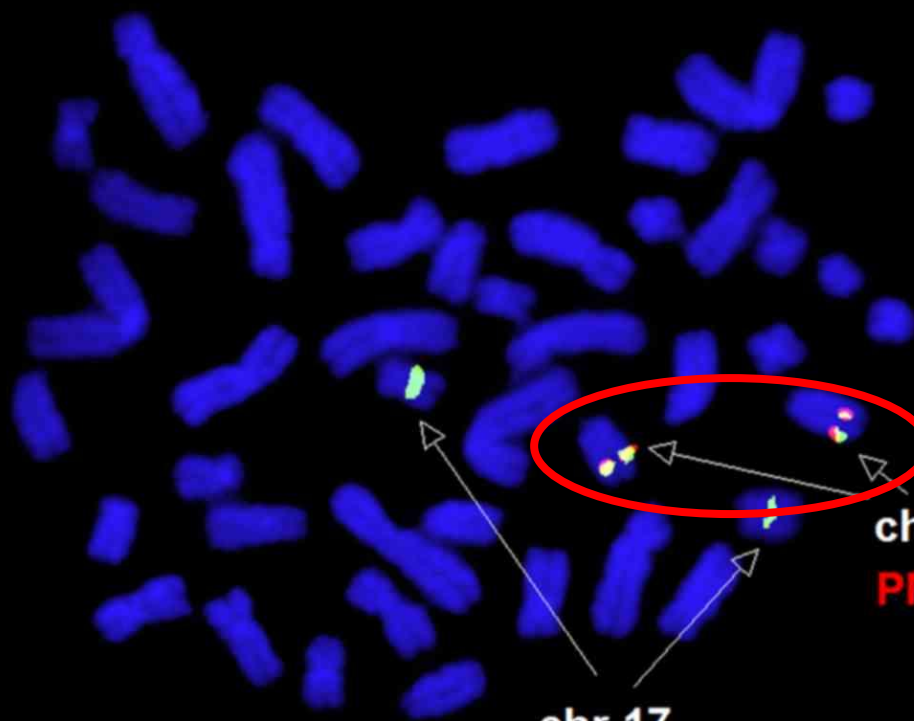
- Treatment includes **all-trans-retinoic acid (ATRA, a vitamin A derivative)**, which binds the altered receptor and causes the blasts to mature .



Acute promyelocytic leukemia (AML, M3 subtype)



PMLx2
RARαx4
PML con RARαx2



chr 17
RARα+

chr 15
PML+ RARα+

	Acute leukemia	Chronic leukemia
Presentation	Days to weeks	months
Course	Rapidly fatal if not treated	Survive for years
Leukemic cells	Undifferentiated/ blasts	differentiated
Maturation arrest	BM failure	No failure

Chronic leukemias

- Neoplastic proliferation of mature circulating cell eg. **lymphocytes (differentiated)** ; characterized by a high WBC count.
- Survive for **years** if not treated
- No BM failure.
- Usually seen in older **adults**.

CML

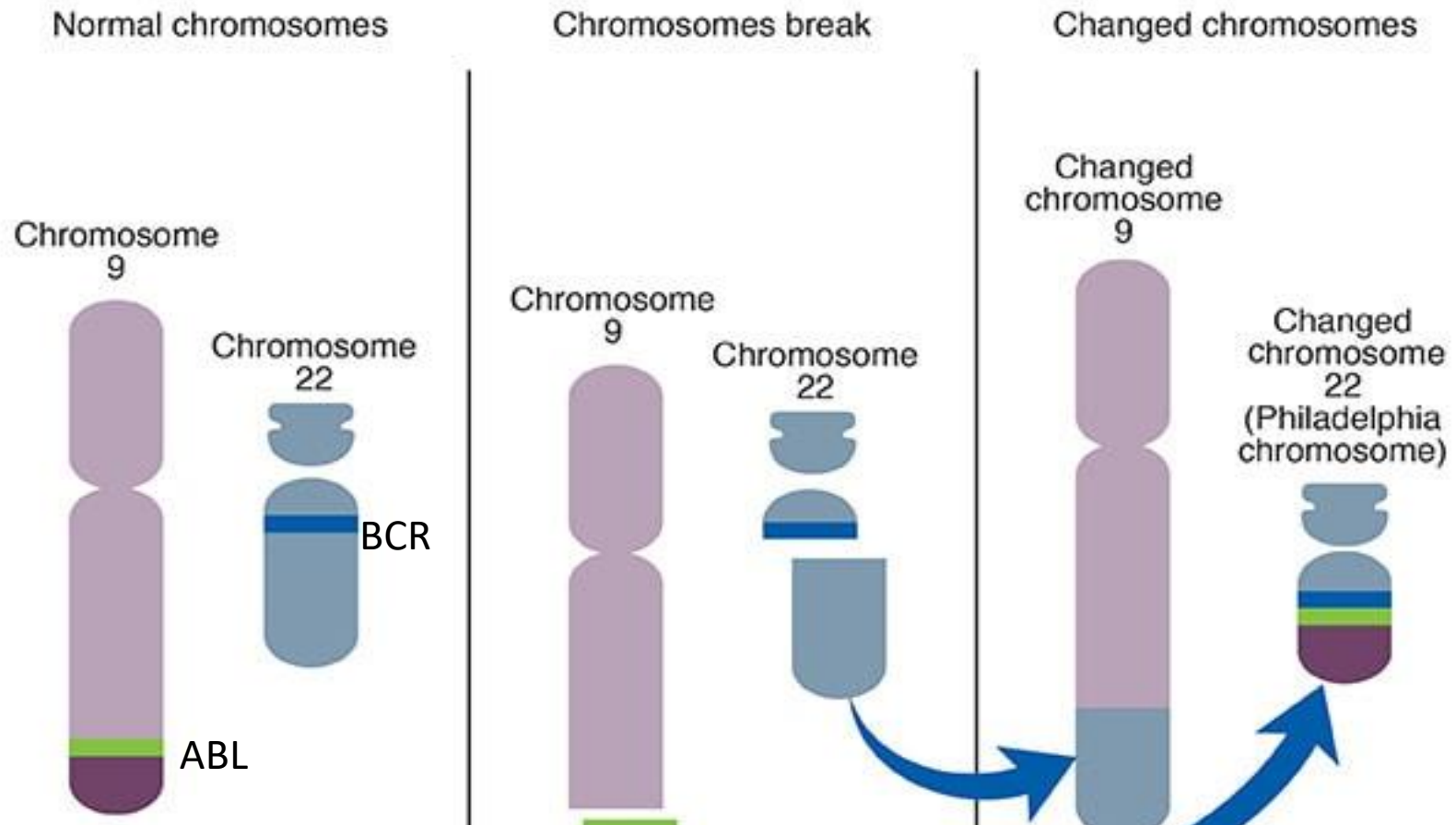
Chronic myeloid leukemia

- Neoplastic proliferation of **mature myeloid** cells, especially **granulocytes**.
- **Philadelphia chromosome t(9,22)**

Clinically

- Nonspecific (easy fatigability, weakness, and weight loss)
- Abdominal distention (**massive splenomegaly** and hepatomegaly)
- Infection and bleeding are not common

Philadelphia chromosome



t(9,22) generates a **BCR-ABL** fusion protein with increased tyrosine kinase activity.
Allowing cell to bypass signals controlling cell differentiation

CML

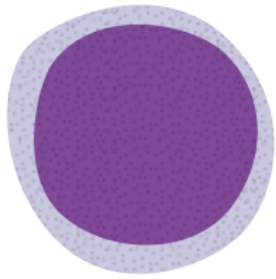
- **BCR-ABL** fusion protein has strong tyrosine kinase activity.
- Allowing cell to bypass signals controlling cell differentiation, and protects leukemic cells from **apoptosis**.
- The early disease course is marked by excessive production of relatively normal blood cells, particularly granulocytes and platelets.

CML

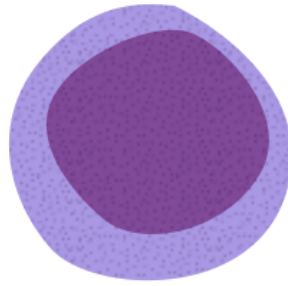
- Enlarging spleen suggests progression to **accelerated phase** of disease; transformation to acute leukemia usually follows shortly thereafter.
- **Blast crises:** transformation to acute leukemia
AML (most of cases) or **ALL**.

CML-labs

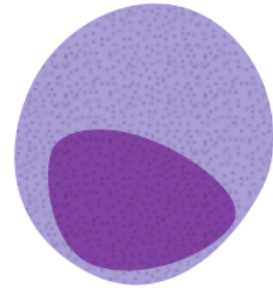
- CBC: **Leukocytosis** ?? > 100,000/ μ L, anemia, thrombocytosis.
- **Blood film** shows **leukocytosis** with **left shift** with immature granulocytes(including bands, metamyelocytes, myelocytes, and promyelocytes) as well as absolute **eosinophilia and basophilia**.
- Circulating blasts may also be seen in chronic phase CML but are usually few (<5%).
- **RBC:** normocytic normochromic type of anemia
PLATELETS: platelet count is normal or moderately increased.



Myeloblast



Promyelocyte



Myelocyte



Metamyelocyte

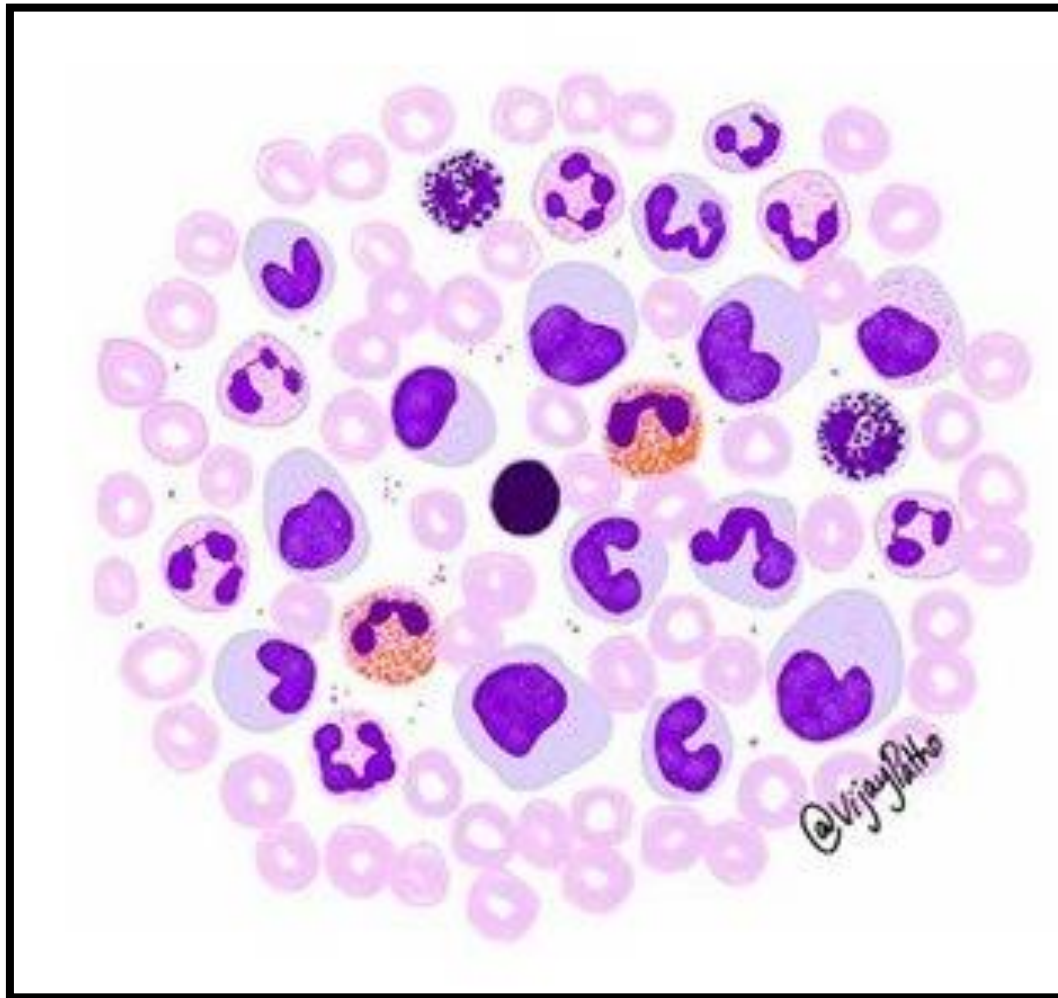


**Banded
Neutrophil**

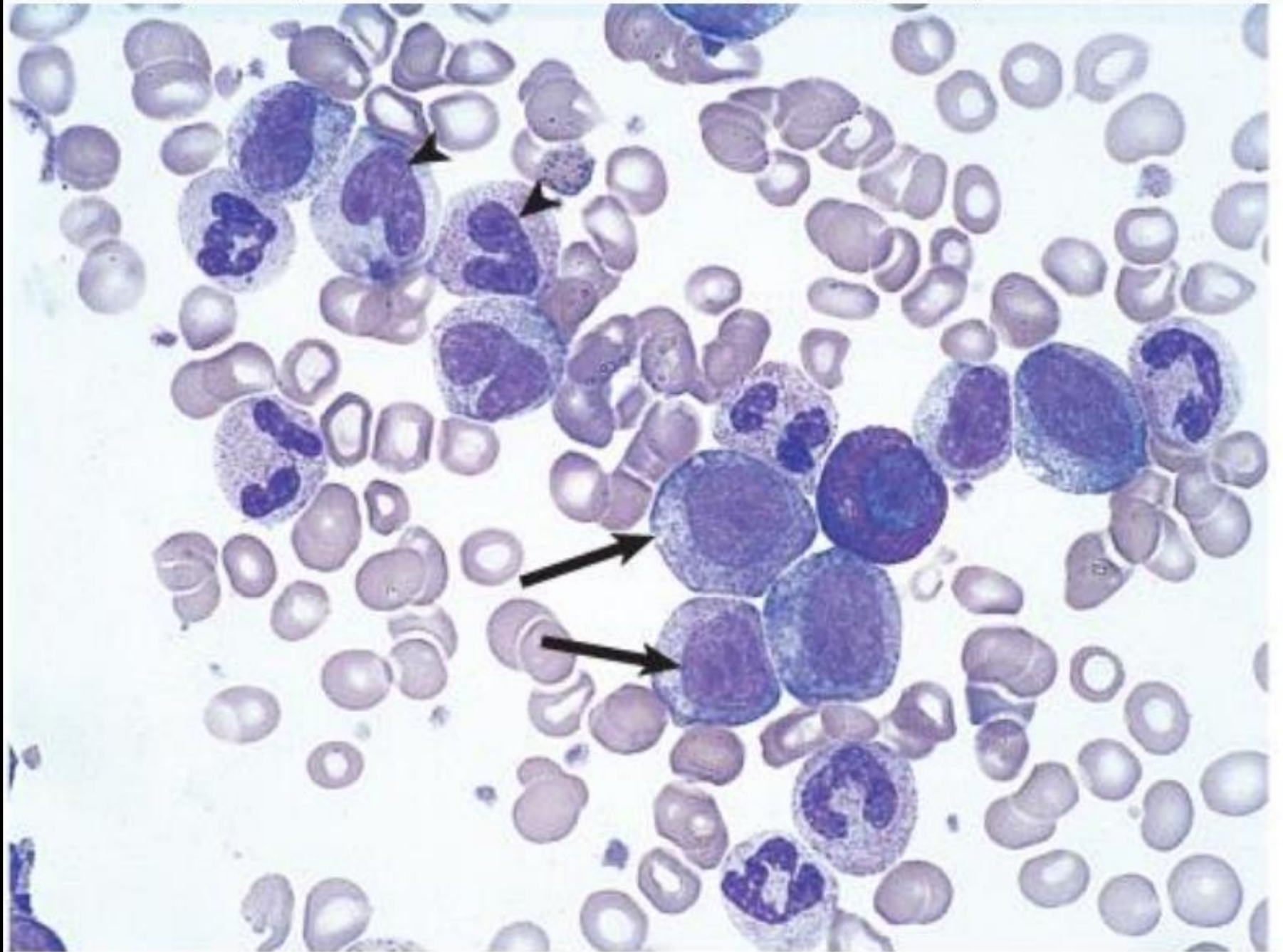


**Mature
Neutrophil**

CML



Myelocytes (arrows) and metamyelocytes (arrowheads)

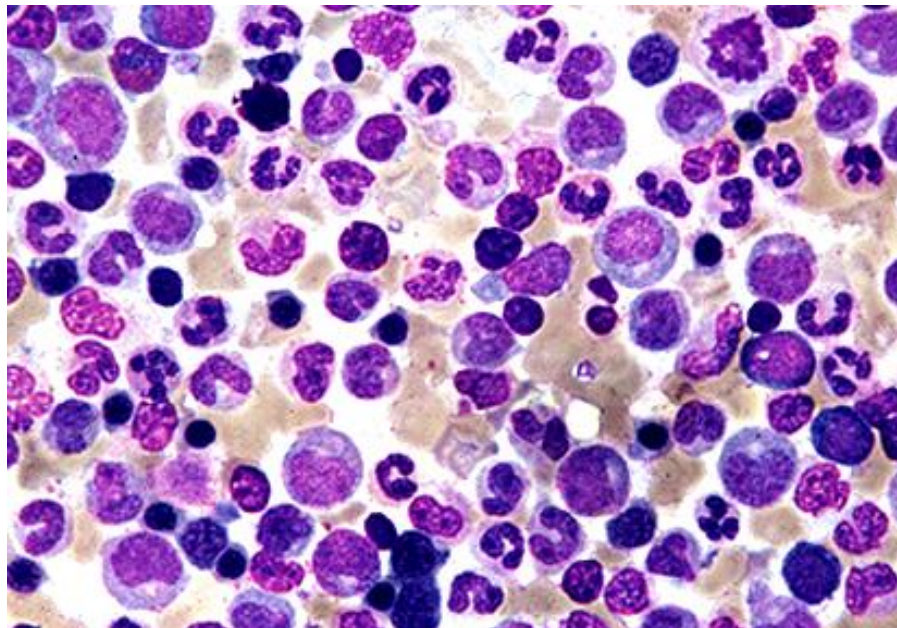


CML vs leukomoid reaction

- **Negative LAP** leukocyte alkaline phosphatase stain.
- Increased **basophils**
- **t(9;22)**
- Elevated serum **vitamin B12**.

CML-labs

- **Hypercellular** bone marrow, with hyperplasia of **granulocytic and megakaryocytic** lineages



CML treatment

- First line treatment is **tyrosine kinase inhibitors (TKI)** imatinib, which blocks tyrosine kinase activity.
- Bone marrow transplantation
- Chemotherapy

	Acute leukemia	Chronic leukemia
Presentation	Days to weeks	months
Course	Rapidly fatal if not treated	Survive for years
Leukemic cells	Undifferentiated/blasts	differentiated
Maturation arrest	BM failure	No failure

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- Neoplastic proliferation of naïve **B cells** that co-express **CD5** and CD20
- Older than age 50 years
- **Most common & the least aggressive** leukemias
- Often does not require therapy

CLL Clinically

- ❑ Often asymptomatic
- ❑ Nonspecific :easy fatigability, weight loss, anorexia
- ❑ Hepatosplenomegaly
- ❑ Generalized lymphadenopathy (**SLL- small lymphocytic lymphoma**)

CLL Clinically

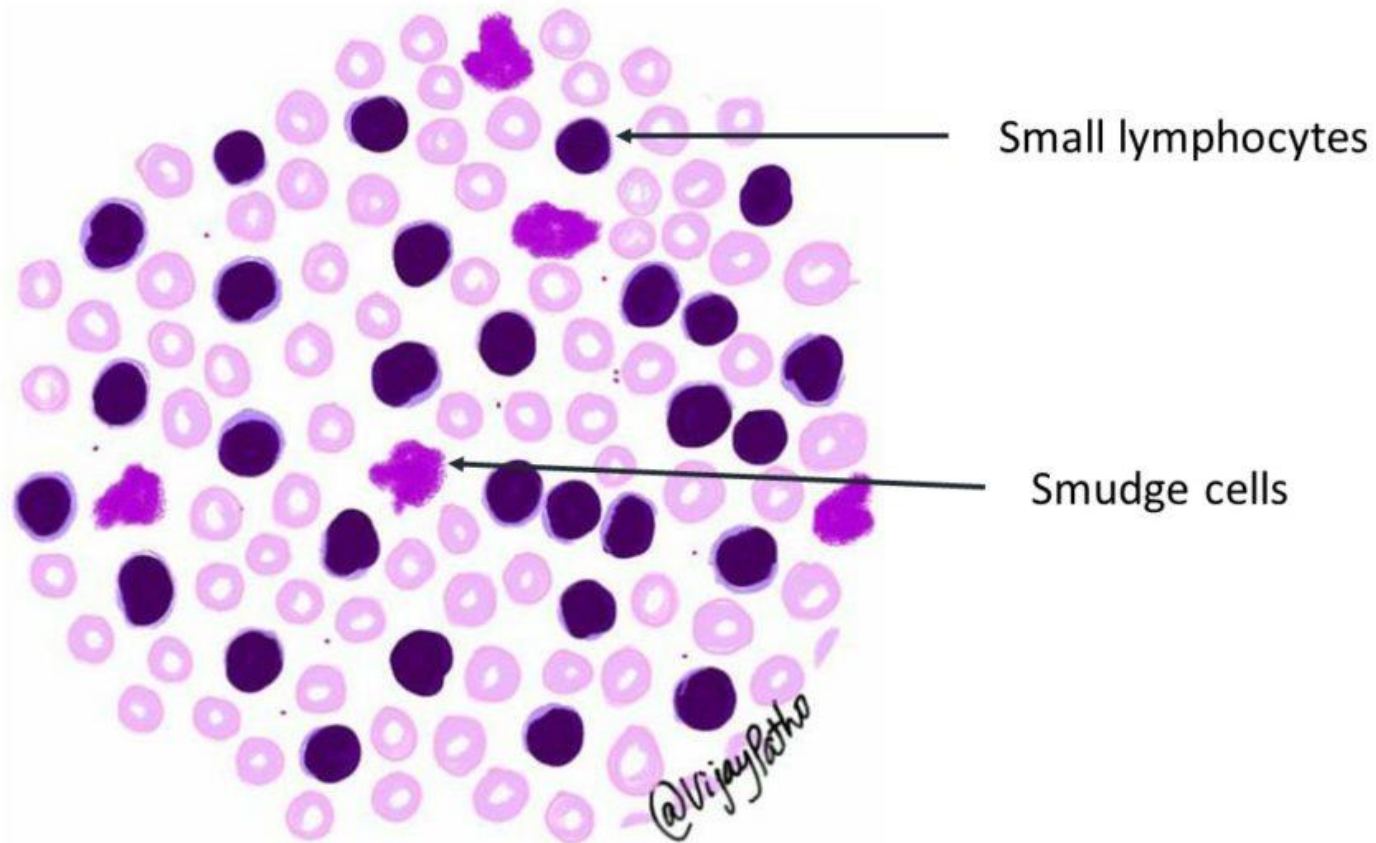
Complications :

- **Hypogammaglobulinemia** :Infection
the most common cause of death in CLL.
- **AIHA**
- **Richter transformation:** Transformation to DLBL,
clinically>>an enlarging lymph node or spleen

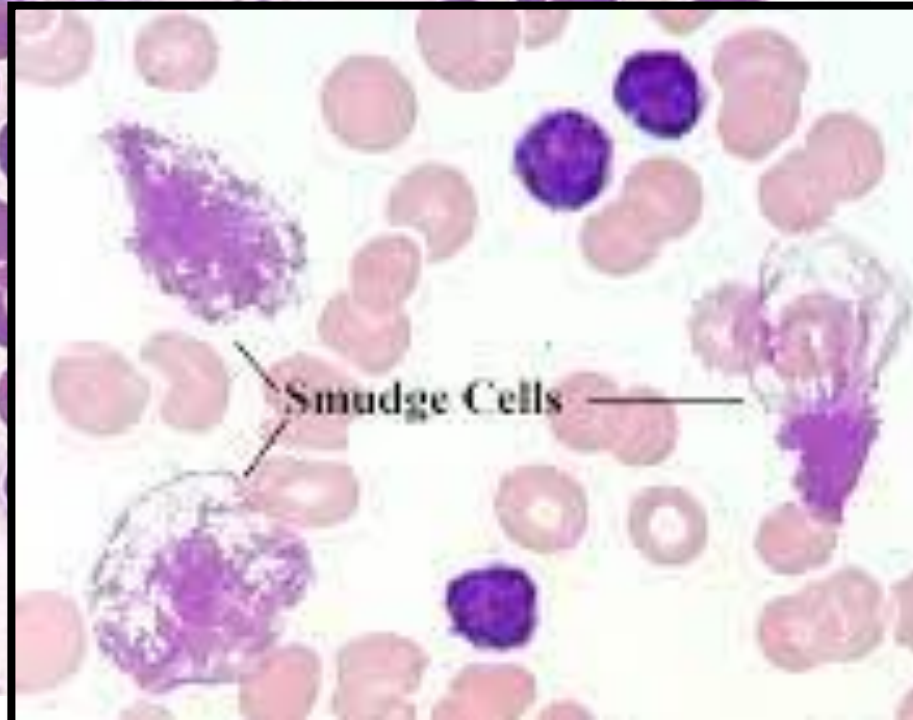
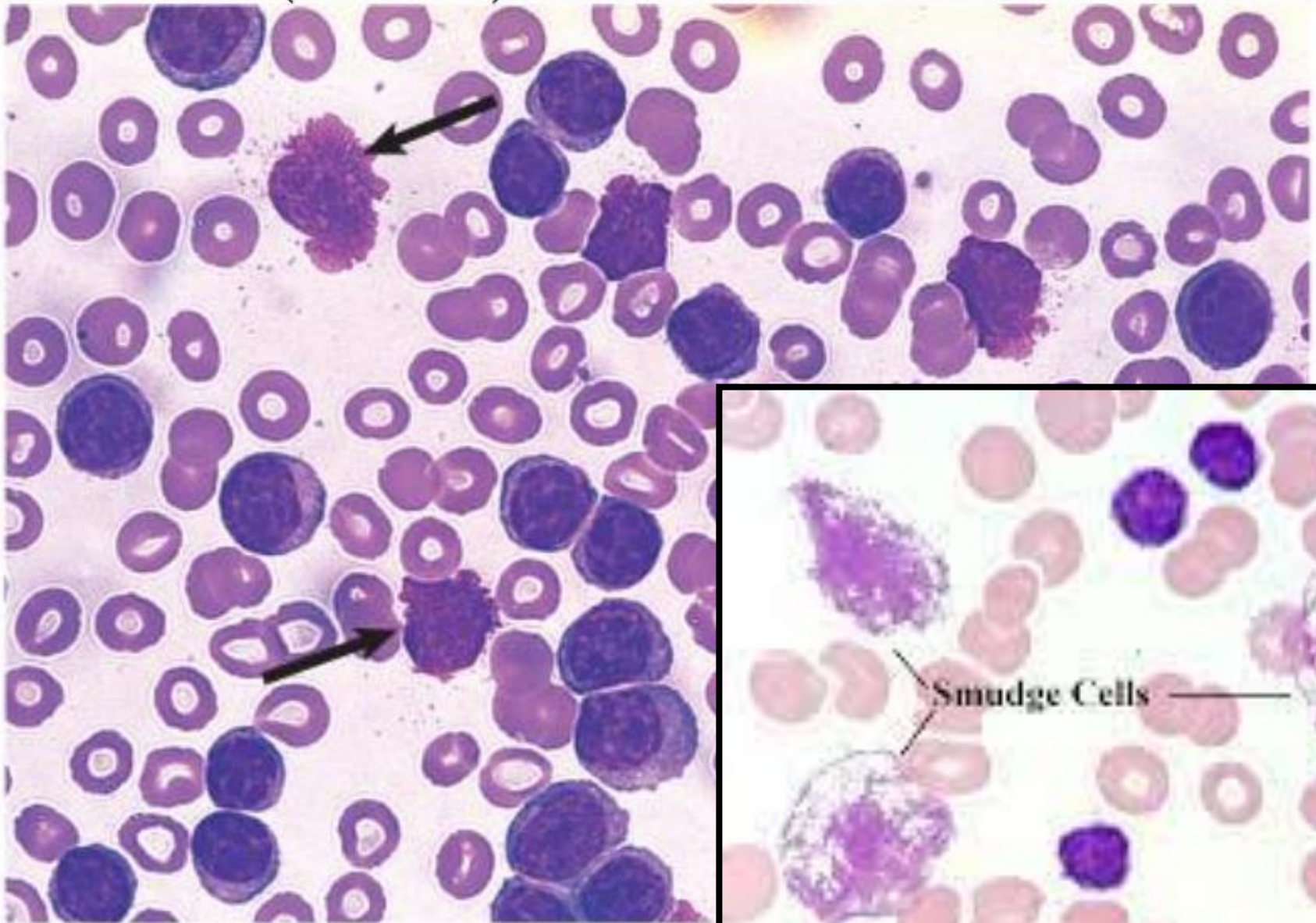
Labs

- Leukocytosis (**lymphocytosis**):
- ALC = $5 - > 300 \times 10^9$
- Anemia (normocytic) and thrombocytopenia
- **Blood film:** lymphocytosis, **smudge** cells
- **Hypercellular BM** , with progressive replacement of normal tissue by lymphocytes

CHRONIC LYMPHOCYTIC LEUKEMIA



Numerous small lymphocytes and **smudge cells** (arrows) are characteristic



Course

- Slowly progressive with a **median survival of 3 to 7 years**
- Many patients **live > 10 years** after diagnosis and die of unrelated causes

Treatment

- Many patients do not require treatment at all.
- Treatment:
 - Chemotherapy
 - BMT
 - mAb



Thank
you

