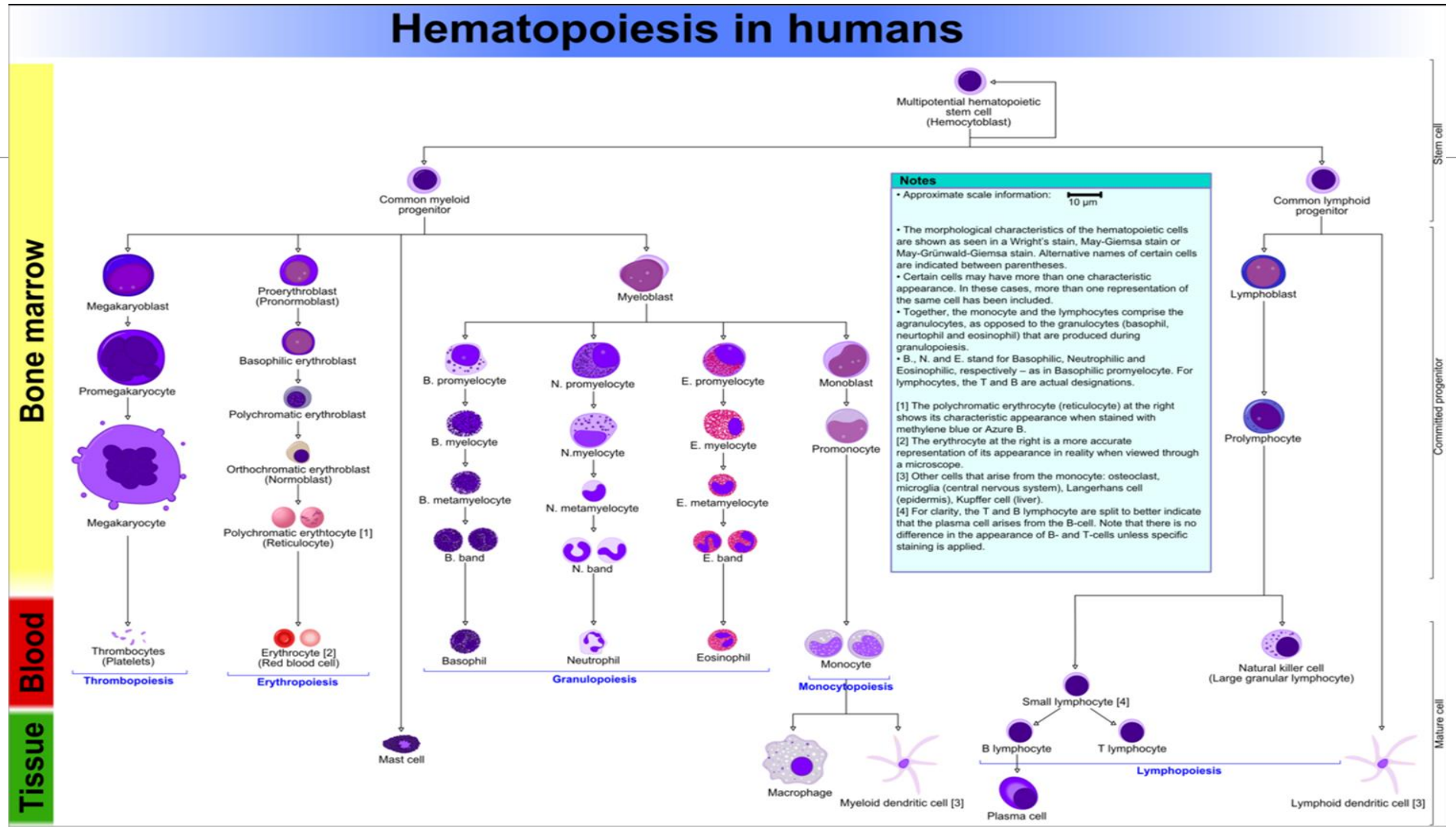
“Hematopoietic And Lymphoid System (HLS)”

Dr. Ola Abu Al Karsaneh


Hematopoiesis in humans
Bone marrow
Blood
Tissue
Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Megakaryoblast
Promegakaryocyte
Megakaryocyte
Thrombocytes (Platelets)
Thrombopoiesis
Proerythroblast (Pronormoblast)
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast (Normoblast)
Polychromatic erythtocyte [1] (Reticulocyte)
Erythrocyte [2] (Red blood cell)
Erythropoiesis
Mast cell
Myeloblast
B. promyelocyte
B. myelocyte
B. metamyelocyte
B. band
Basophil
N. promyelocyte
N.myelocyte
N. metamyelocyte
N. band
Neutrophil
E. promyelocyte
E. myelocyte
E. metamyelocyte
E. band
Eosinophil
Granulopoiesis
Monoblast
Promonocyte
Monocyte
Monocytopoiesis
Macrophage
Myeloid dendritic cell [3]
Notes
• Approximate scale information: 10 µm
• The morphological characteristics of the hematopoietic cells are shown as seen in a Wright's stain, May-Giemsa stain or May-Grünwald-Giemsa stain. Alternative names of certain cells are indicated between parentheses.
• Certain cells may have more than one characteristic appearance. In these cases, more than one representation of the same cell has been included.
• Together, the monocyte and the lymphocytes comprise the agranulocytes, as opposed to the granulocytes (basophil, neurtophil and eosinophil) that are produced during granulopoiesis.
• B., N. and E. stand for Basophilic, Neutrophilic and Eosinophilic, respectively -- as in Basophilic promyelocyte. For lymphocytes, the T and B are actual designations.
[1] The polychromatic erythrocyte (reticulocyte) at the right shows its characteristic appearance when stained with methylene blue or Azure B.
[2] The erythrocyte at the right is a more accurate representation of its appearance in reality when viewed through a microscope.
[3] Other cells that arise from the monocyte: osteoclast, microglia (central nervous system), Langerhans cell (epidermis), Kupffer cell (liver).
[4] For clarity, the T and B lymphocyte are split to better indicate that the plasma cell arises from the B-cell. Note that there is no difference in the appearance of B- and T-cells unless specific staining is applied.
Lymphoblast
Prolymphocyte
Small lymphocyte [4]
B lymphocyte
T lymphocyte
Lymphopoiesis
Plasma cell
Natural killer cell (Large granular lymphocyte)
Lymphoid dendritic cell [3]
Stem cell
Committed progenitor
Mature cell

Nonneoplastic Disorders Of White Blood Cells

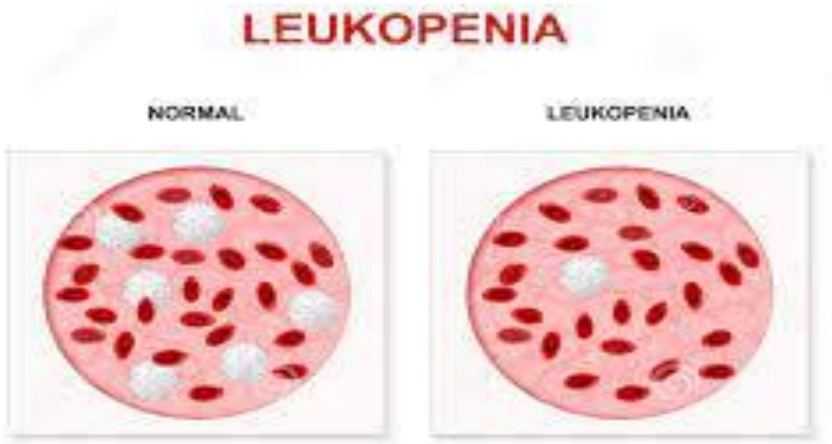
❑ Leukopenia

- Is a **decrease** in the leukocyte count in the blood.

- Mostly, from a decrease in granulocytes, **lymphopenia is much less common**.

❑ Lymphopenia :

- Immunodeficiency disease (HIV) infection.
- Therapy with corticosteroids.
- Certain viral infections.



Neutropenia/Agranulocytosis:

Neutropenia: a reduction in the number of neutrophils in the blood.

Agranulocytosis: a clinically significant reduction in neutrophils.

Pathogenesis:

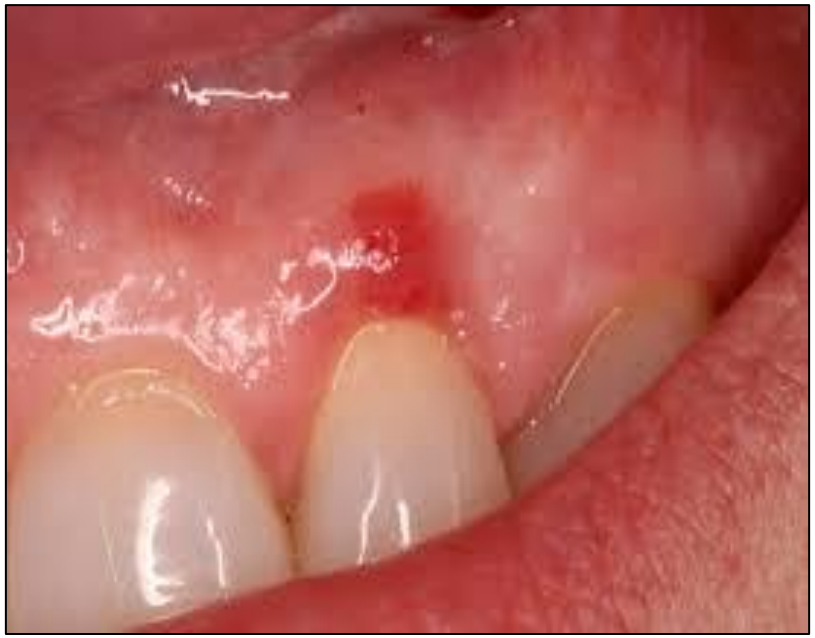
1. **Decreased granulocyte production**: mostly by marrow hypoplasia, e.g. by chemotherapy, drugs, or infiltrative tumor.

2. **Increased granulocyte destruction**: in immune-mediated injury by drugs or in overwhelming infections, resulting from increased peripheral use or due to splenomegaly.

Clinical Features:

- Increased risk for severe bacterial and fungal **infections.**

- Systemic symptoms as malaise, chills, and fever.
- Commonly as necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa or pharynx.



Morphology:

- **The alterations in the bone marrow depend on the cause**.

- Compensatory marrow hypercellularity when there is excessive neutrophil destruction.
- Chemotherapy drugs reduce the number of elements from all lineages.
- Drugs that selectively suppress granulocytopoiesis are associated with decreased numbers of granulocytic precursors and preservation of erythroid elements and megakaryocytes

❑ Reactive Leukocytosis

- An **increase** in the number of white cells in the blood.

- Classified according to the white cell series that is affected.

❑ Causes of 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

Infectious Mononucleosis:

-An acute, self-limited disease of adolescents and young adults caused by **EBV.**

- It is associated with **lymphocytosis.**

❑ Clinical features:

- Classically, fever, sore throat, and lymphadenitis.
- Or atypical presentations as little or no fever and only lymphadenopathy.

Pathogenesis:

- The virus initially infects oropharyngeal epithelial cells and then spreads to underlying lymphoid tissue.

- Mature B cells that are infected become “activated,” by several **viral proteins,** proliferate and disseminate in the circulation, and secrete antibodies with unusual specificities ⟹ The host T cell response controls the proliferation of EBV-infected B cells and the spread of the virus, in addition early in the course of the infection, IgM antibodies are formed against viral antigens. Later the serologic response shifts to IgG antibodies, which persist for life.

- Virus-specific cytotoxic CD8+ T cells appear in the circulation as atypical lymphocytes.

❑ Morphology:

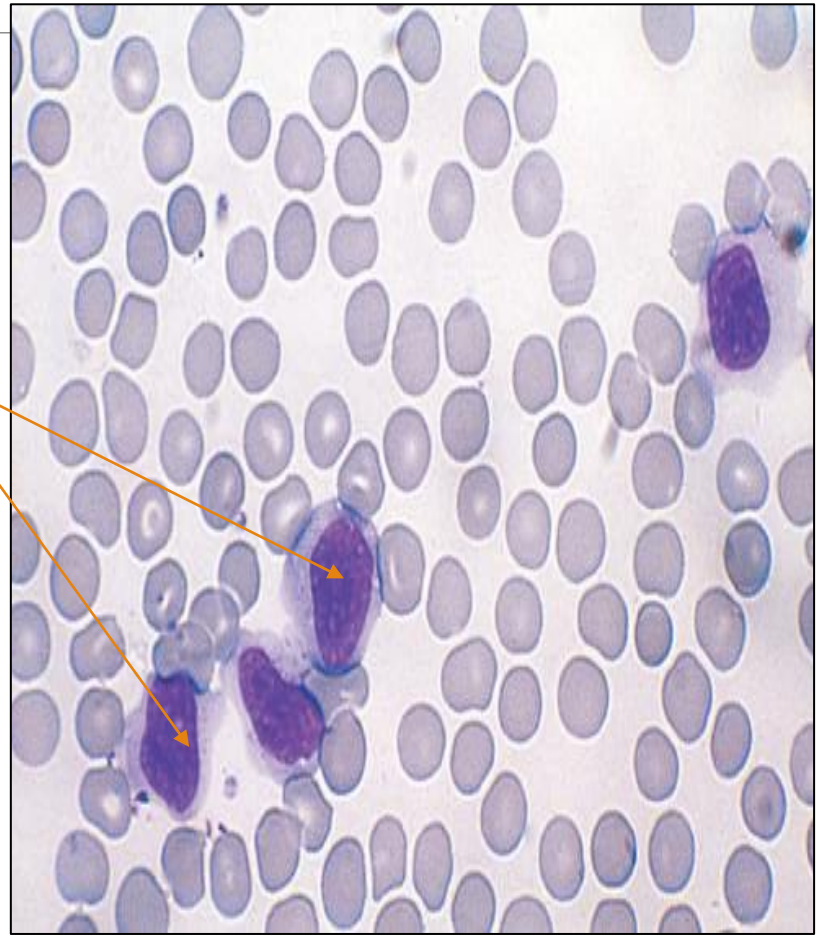
❖ **Peripheral blood: leukocytosis**; more than half of these cells are large **atypical lymphocytes (CD8+ T cell)**.

❖ **Lymph nodes: Lymphadenopathy.**

- Histology: the enlarged nodes are flooded by atypical lymphocytes in the **paracortical (T cell)** areas.

❖ **Spleen:** Enlarged with heavy infiltration of atypical lymphocytes

❖ **Liver:** Atypical lymphocytes usually also infiltrate the portal areas and sinusoids



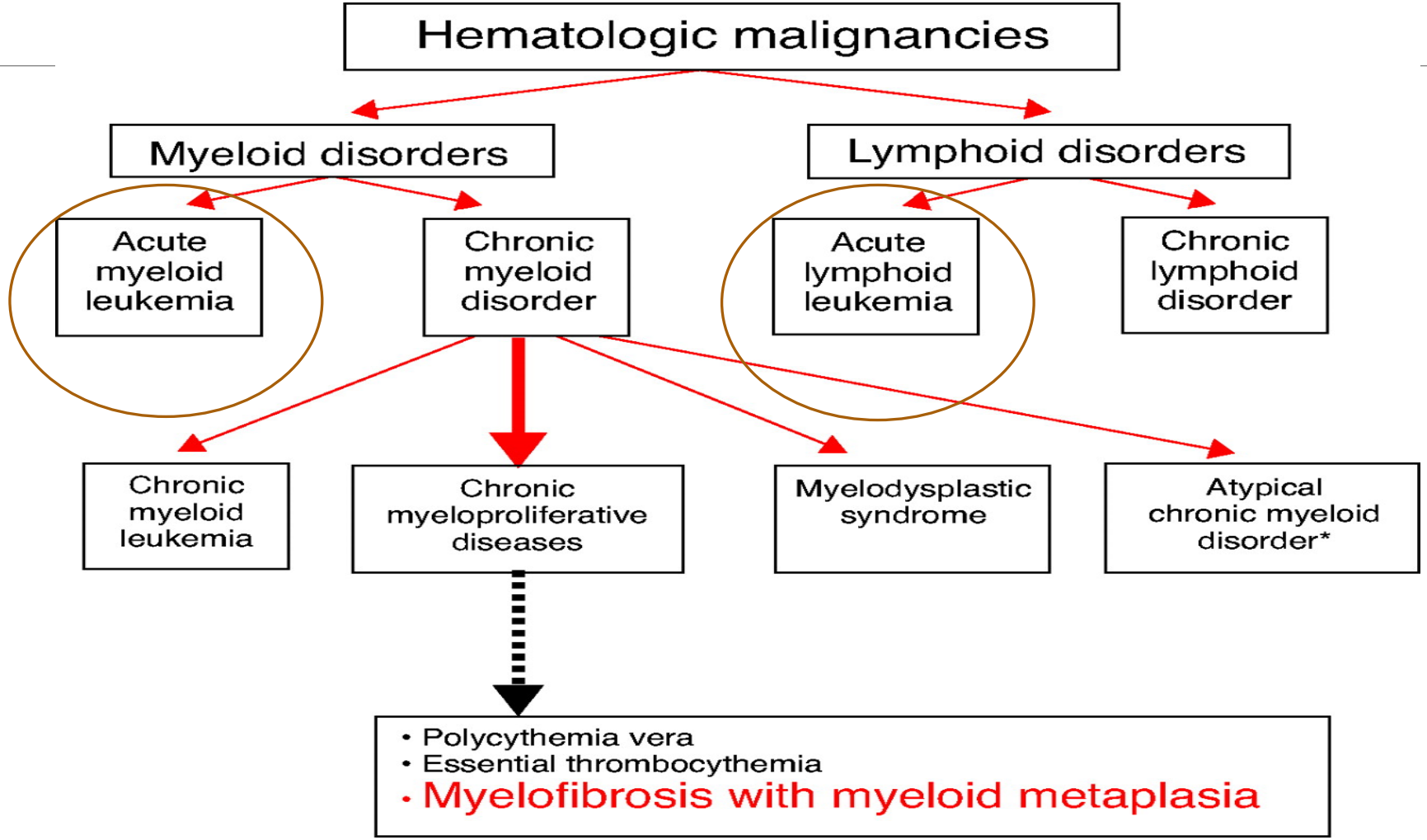
❑ Diagnosis

(1) The presence of atypical lymphocytes in the peripheral Blood

(2) A positive heterophil reaction (Monospot test)

(3) A rising titer of antibodies specific for EBV antigens

Neoplastic Proliferations Of White Cells



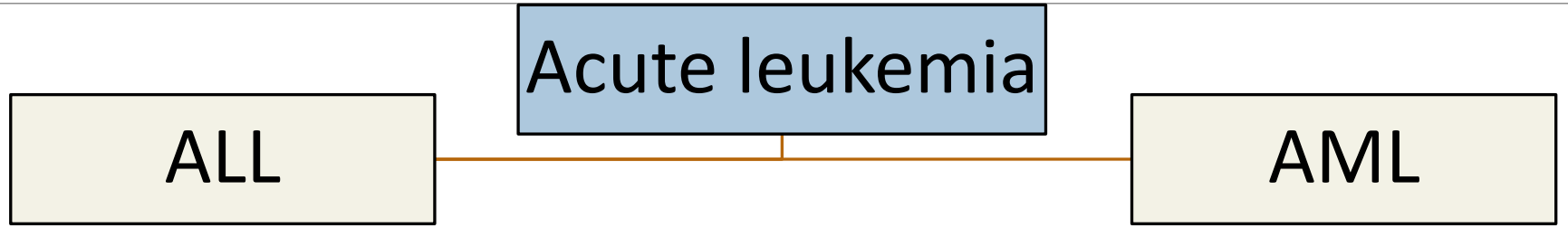
Acute Leukemia

-**Leukemia**: Tumors that involve the **bone marrow and peripheral blood predominantly**.

- Malignant clonal expansion of hematopoietic or lymphoid cells associated with **early stages of differentiation** and characterized by:

- Poor response to normal regulatory mechanisms
- Decreased capacity for normal differentiation
- A growth advantage over normal hematopoietic cells

Epidemiology



- 70% are AML
- 1/3 of all cancers in children

  - 80% are ALL & 20% are AML

- **ALL** is a childhood disease
- **AML** is an adulthood disease.

Precursor B- & T-cell Acute Lymphoblastic Leukemia/Lymphoma (ALL)

- Definition:

Malignant clonal expansion of **immature** pre-B or T lymphoid cells **(lymphoblasts)** involving bone marrow, blood, and occasionally involving nodal and extranodal sites (lymphoblastic lymphoma).

- **Leukemia if more than 20% lymphoblasts in BM or blood**
- **Lymphoma if mass lesion present, and less than 20% lymphoblasts in BM or blood**

Epidemiology:

- Aggressive tumors occur predominantly in **children & young adults**.
- About 85% are B-ALLS, typically present as acute "leukemias" (peak at age of 3).
- The less common T-ALLS present in adolescent males as thymic "Lymphomas" as a mediastinal mass.
- ALL is the **most common cancer in children**.
- More in whites and boys.

Etiologic associations

Chronic exposure to chemicals
Ionizing radiation
Immunodeficiency states

Pathogenesis:

- Stems from chromosomal aberrations that dysregulate the function of transcription factors that are required for the normal differentiation of B and T cell progenitors.
- Also, mutations that increase tyrosine kinase activity and cell proliferation in a growth factor–independent fashion

ALL Genetics

B- ALL:

- Hyperdiploidy : ≥ 50 chromosomes/ cell
- t (12;21)
- 25% of adult pre-B cell tumors harbor t (9;22) involving the ABL and BCR genes.

T –ALL: diverse chromosomal aberrations.

•Clinical Features:

Are primarily due to replacement of normal hematopoietic elements by blasts leading to **paucity** of:
Red cells
Platelets
Normal white cells

- Anemia and pallor
- Weakness and fatigue
- Fever
- Thrombocytopenia and bleeding
- Bone pain
- Hepatosplenomegaly and generalized lymphadenopathy (caused by the dissemination of the leukemic cells)
- CNS involvement from the meningeal spread.

(headache, vomiting)

- Testicular involvement is common in ALL

- **Diagnosis:**

  - **CBC**

    - Anemia.

    - Thrombocytopenia.

    - WBC count variable :

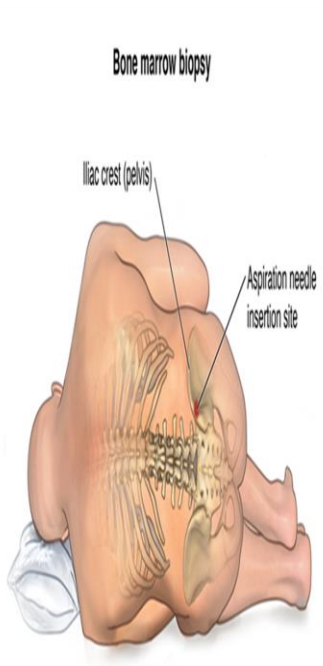
      Leukocytosis with blasts (>25%)

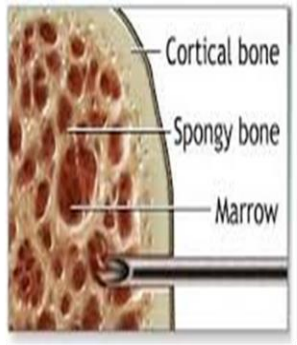
      Normal or decreased WBC (50%)

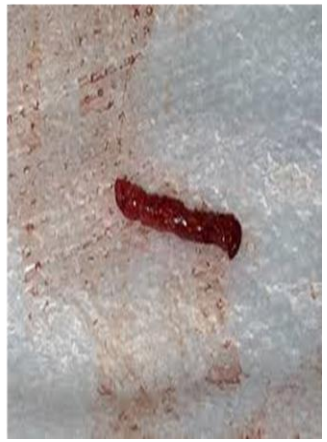
      Neutropenia is a common finding

  - **Peripheral blood smear**

  - **Bone marrow aspiration and biopsy.**







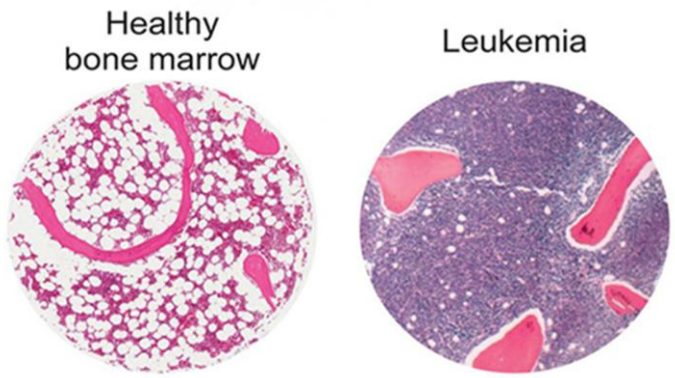
- Morphology:

- BP: Identifications of blasts.

- Bone marrow: is hypercellular and packed with **lymphoblasts**

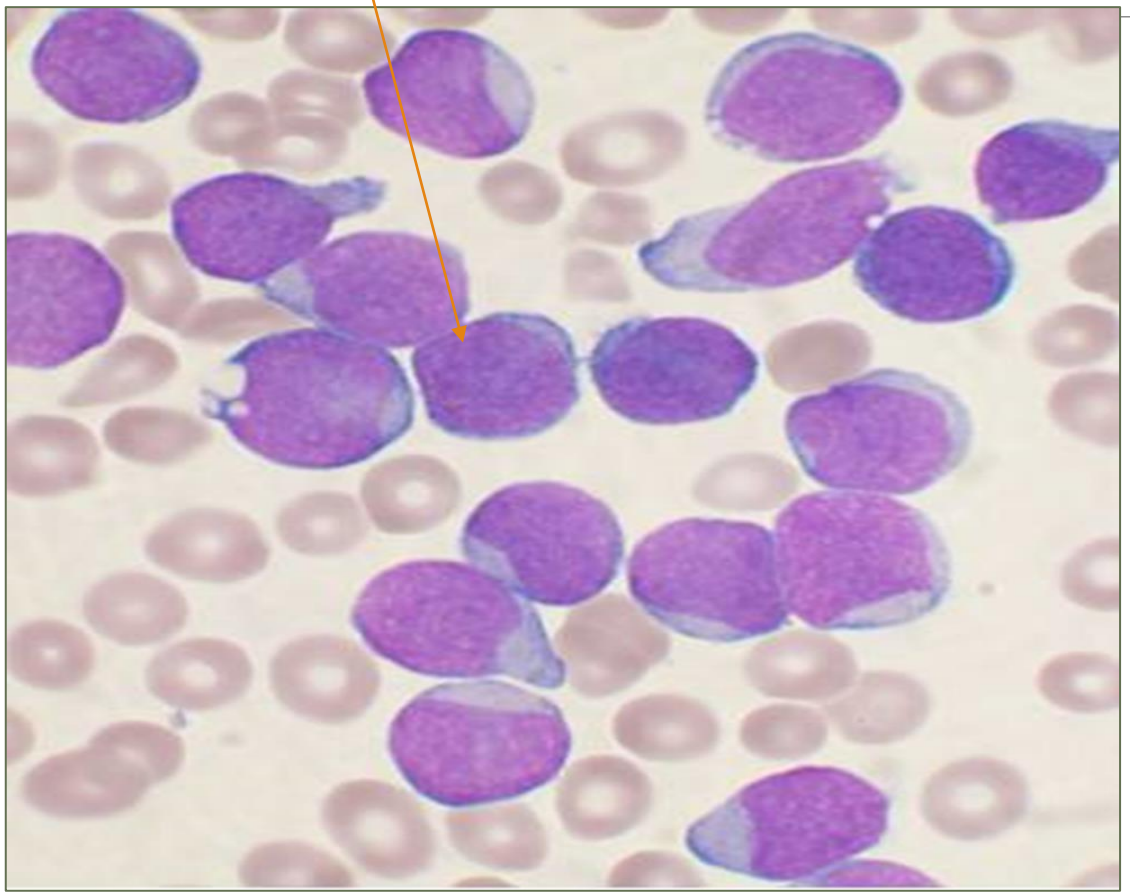
❖ Scant **A**granular basophilic cytoplasm and nuclei with delicate, finely stippled chromatin and small nucleoli.

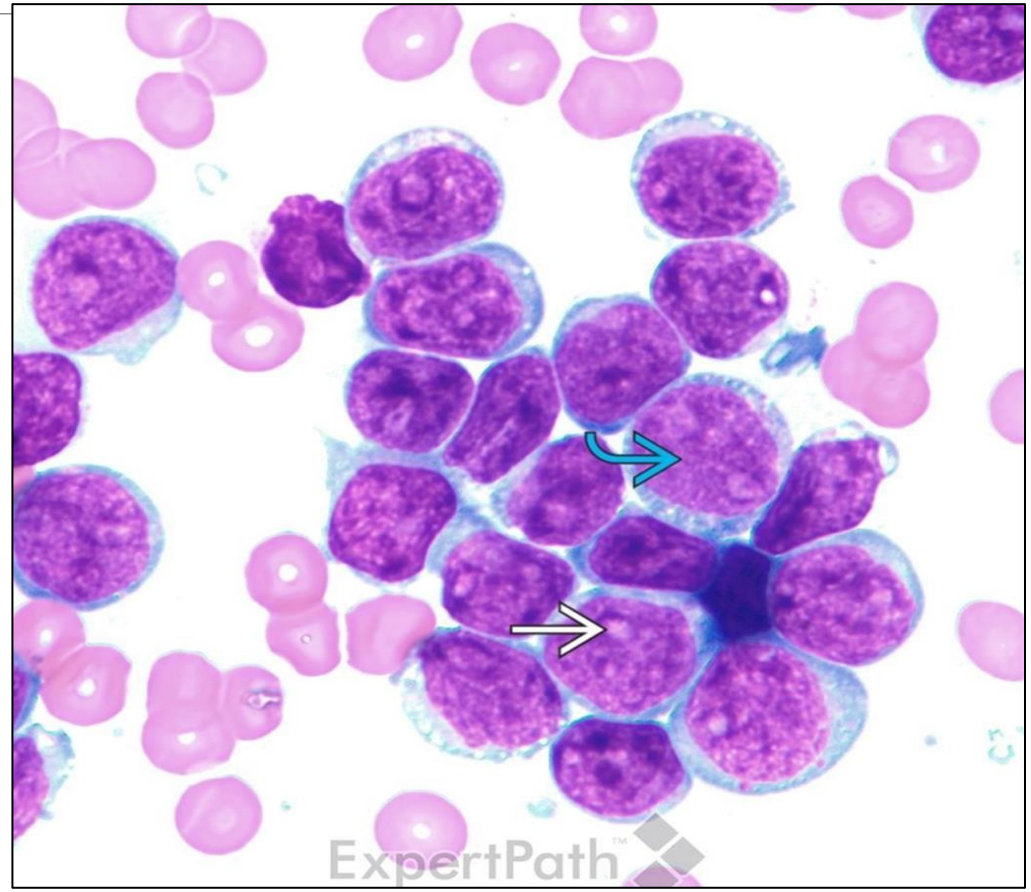
❖The cytoplasm has glycogen stains positive with PAS stain.



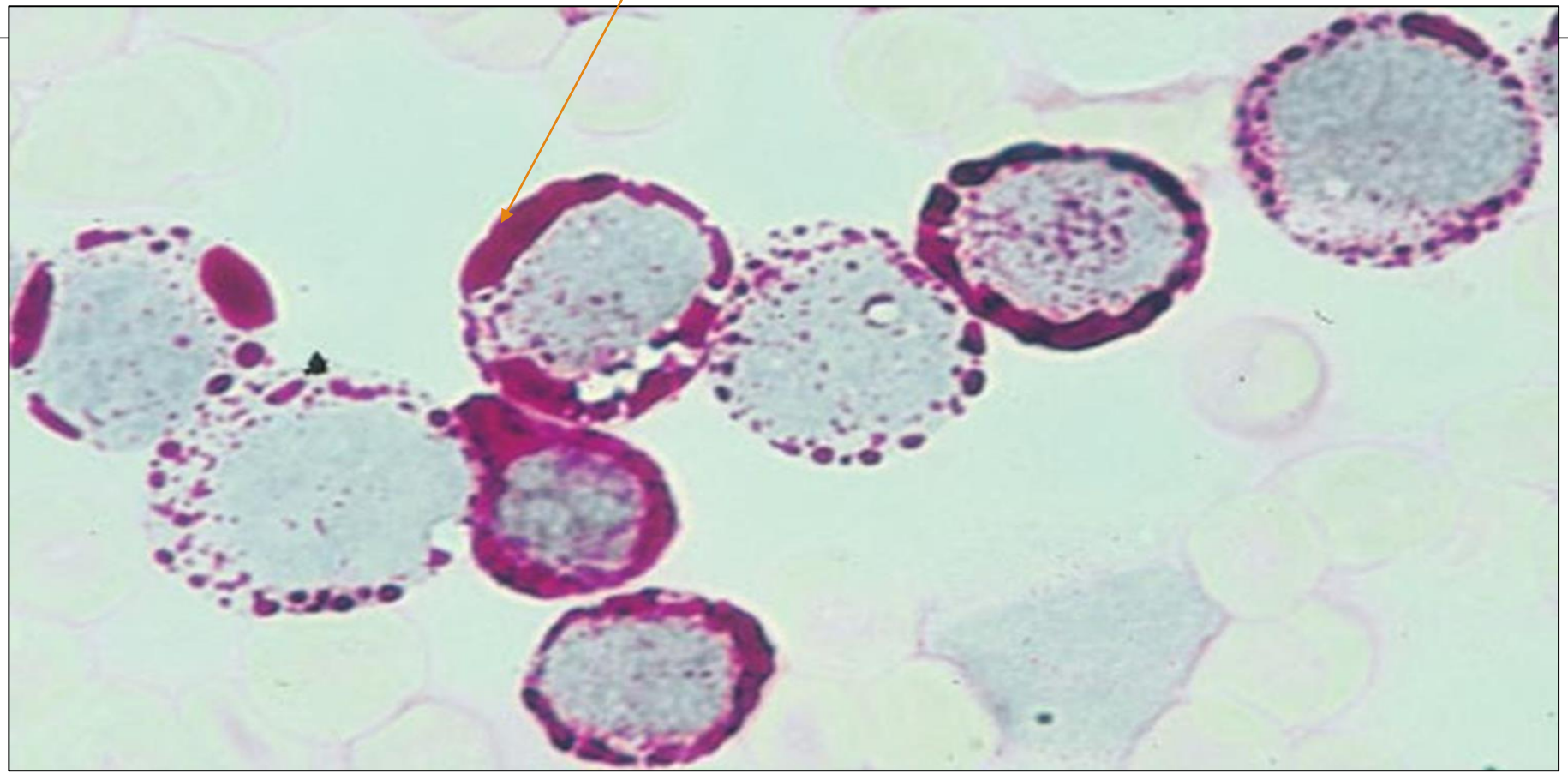
- **Mediastinal masses** occur in T-ALLS.
- High mitotic rate.
- The appearance of the blasts is identical in pre-B and pre-T ALLs
- For this reason, definitive diagnosis relies on stains specific for B AND T cell antigens.

ALL (lymphoblasts):with high N/C ratio, fine chromatin (curved arrow), small nucleoli (white solid arrow), and basophilic cytoplasm.





Lymphoblasts: Positive PAS cytoplasmic stain.

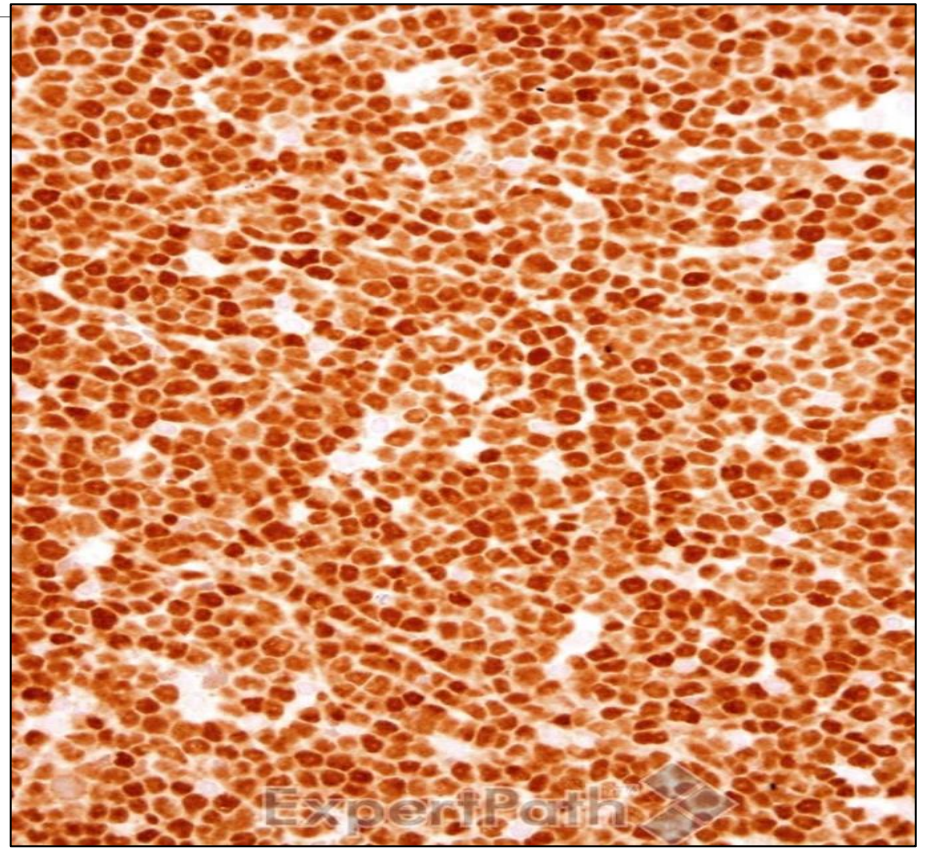


- Immunophenotyping:

- Performed by IHC on tissues:
- B-ALL (85%)
  - **TdT+** ,CD10+, **CD19+**, **CD20+**, CD22+, **CD79+**, PAX5+
- T-ALL (15%)
  - **TdT+**, CD2+, **CD3+**, **CD5+**, CD7+

Terminal deoxynucleotidyl transferase (TdT), an enzyme specifically expressed in pre-B and pre-T cells.

+ve TDT



- ## Prognosis:

  - Generally, has an **excellent prognosis** with aggressive chemotherapy, but rapidly fatal if untreated.
  - In children with chemotherapy, 95% remission rate and 75-85% cure rate (if **favorable prognostic features**).
  - Only 35% to 40% of affected adults are cured.

Factor	Favorable	Unfavorable
Age	2-10	<2, >10
WBC count	<50,000	>50,000
# chromosomes	Hyperdiploidy (>50)	Hypodiploidy (<44)
Cytogenetics	T(12, 21)	T(4,11), t(9.22), t(1,19)
CNS disease	Absent	Present
CD10	Positive	negative

Acute Myeloid Leukemia (AML)

- Malignant clonal expansion of cells blocked at an early stage of myeloid cell development (**immature myeloid cells (myeloblasts))** that accumulate in the marrow and frequently circulate in the peripheral blood.

Myeloid blasts or promyelocytes make up more than 20% of the bone marrow cellular component.

- Older adults (50 yrs).

❖ Pathogenesis:

- Most harbor **mutations** in **genes** encoding **transcription factors** required **for normal myeloid cell differentiation, which** interferes with the differentiation of early myeloid cells, leading to the accumulation of myeloid precursors (blasts) in the marrow.

e.g t(15,17)⟶ results in the fusion of ***(RARA)*** gene and the ***PML*** gene. The chimeric gene produces a PML/RARA fusion protein that blocks myeloid differentiation **at the promyelocytic stage.**

❑ All-*trans* retinoic acid **(ATRA)** overcomes this block and induces the neoplastic promyelocytes to differentiate into neutrophils.

- Mutations that lead **to activation of growth factor signaling pathways,** which increase cell proliferation.

❖ Clinical Features

- Usually related to the replacement of normal marrow elements by leukemic blasts.

- Fatigue

- Pallor

- Infections (fever)

- Abnormal bleeding (Cutaneous petechiae, ecchymoses, serosal hemorrhages into the linings of the body cavities and viscera)

- Splenomegaly and lymphadenopathy generally are less prominent than in ALL

- Rarely, AML mimics a lymphoma by manifesting as a discrete tissue mass (a so-called “granulocytic sarcoma”).

- Tumors with monocytic differentiation often infiltrate the skin (leukemia cutis) and the gingiva

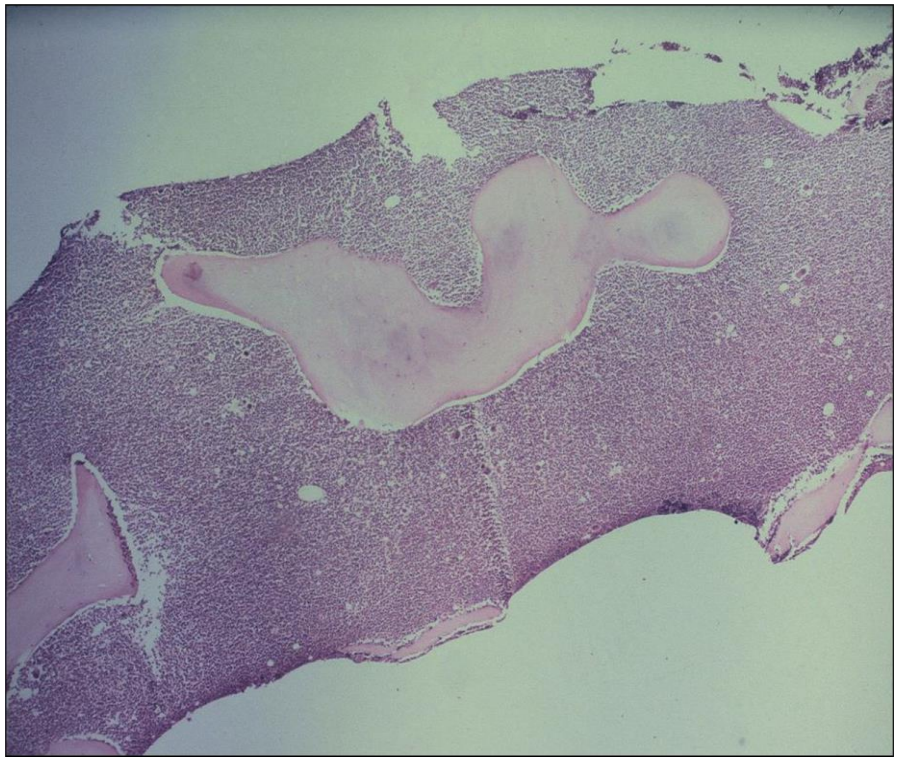
❖ Morphology

- Myeloid blasts make up **more than 20%** of the bone marrow cellularity.

- **Myeloblasts** have delicate nuclear chromatin, three to five nucleoli, and fine azurophilic cytoplasmic granules (peroxidase positive).

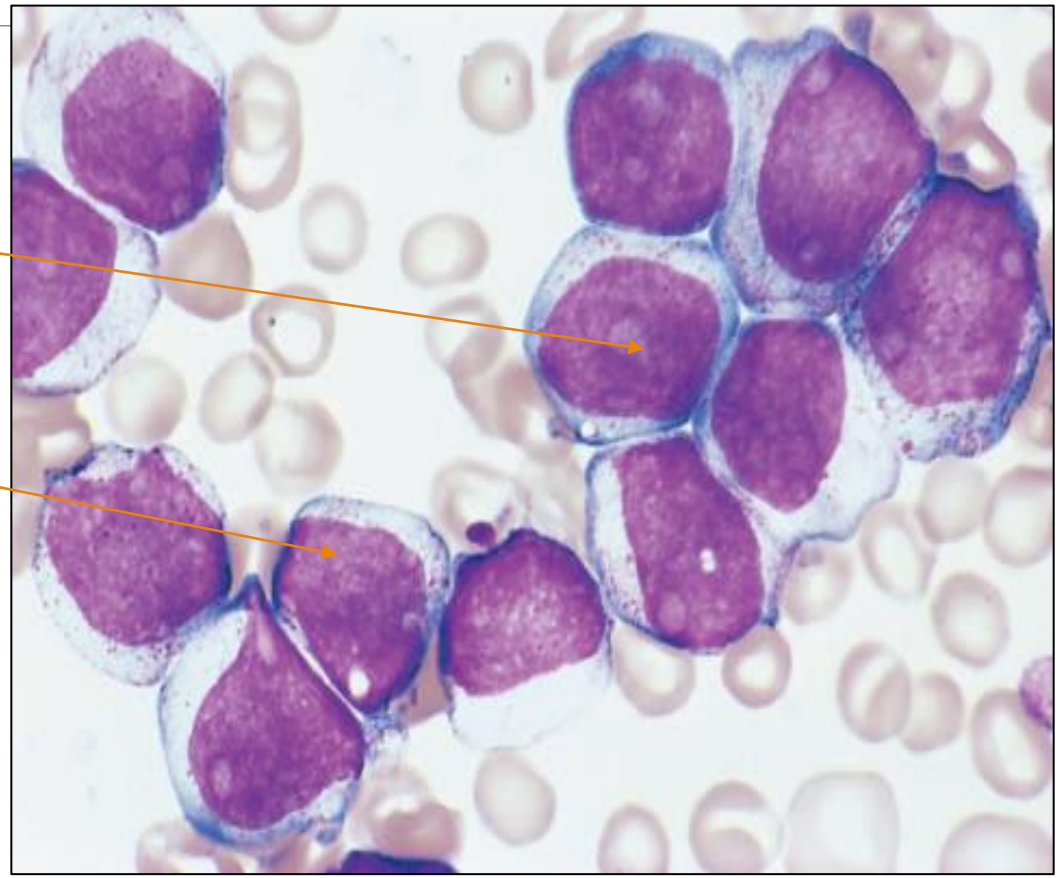
- **Auer rods,** distinctive red-staining rodlike structures, may be present in myeloblasts or more differentiated cells; they are particularly **numerous** in **acute promyelocytic leukemia (M3).**

- **Auer rods are specific for neoplastic myeloblasts** and thus are a helpful diagnostic clue when present.



AML

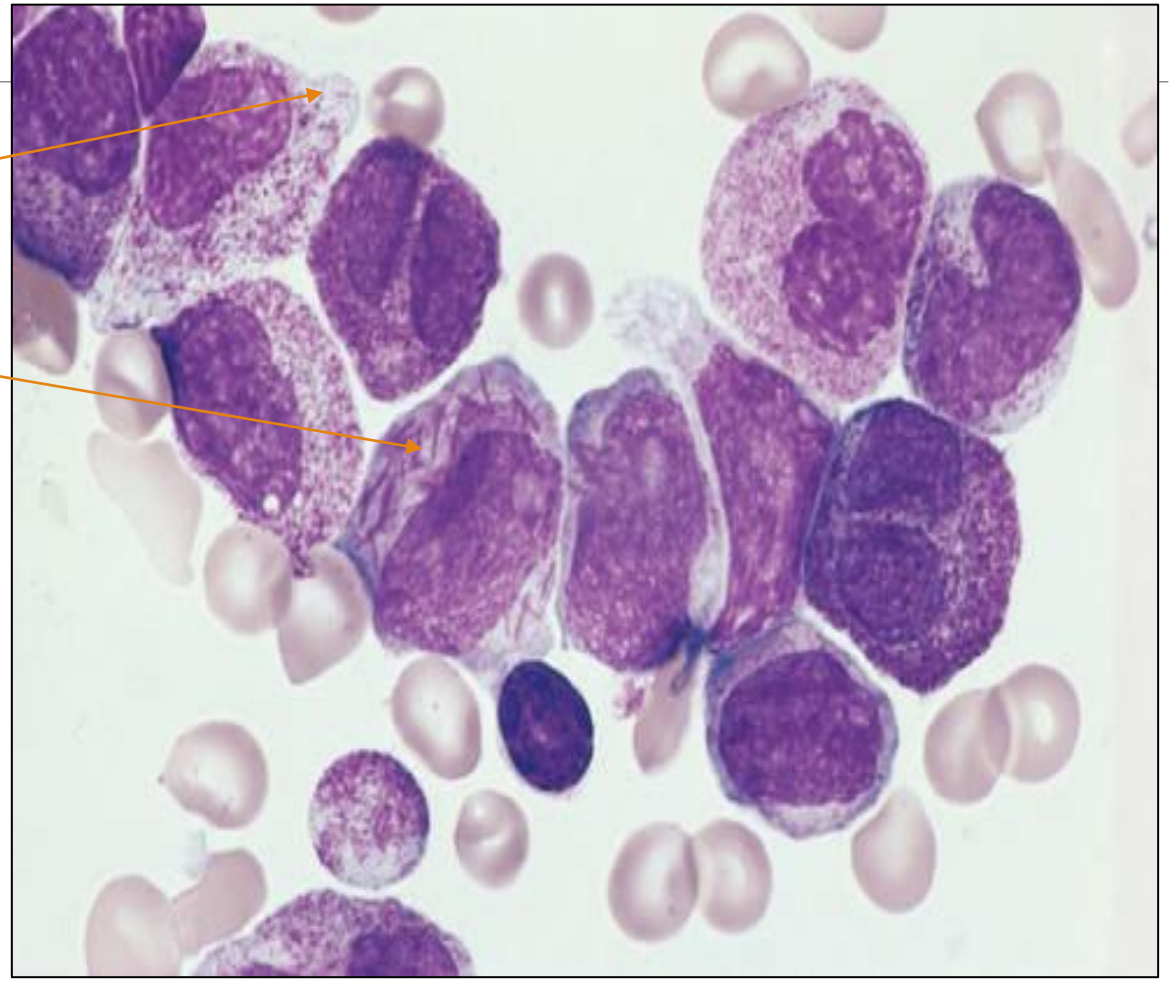
Myeloblasts with delicate nuclear chromatin, prominent nucleoli, and fine azurophilic cytoplasmic granules.

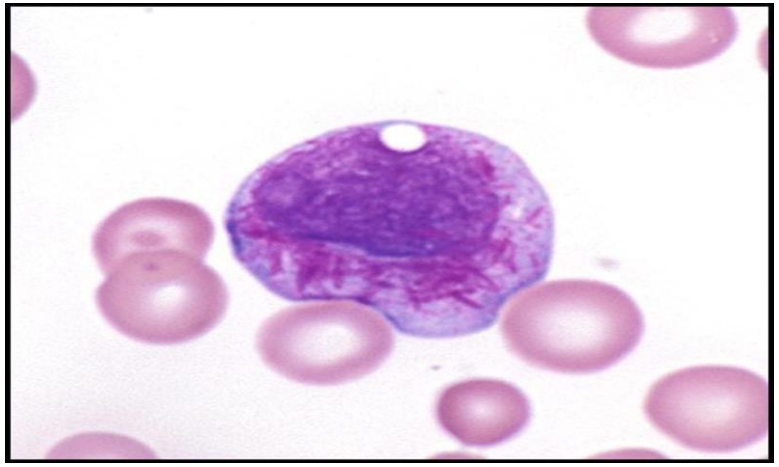


Acute promyelocytic leukemia—bone marrow aspirate

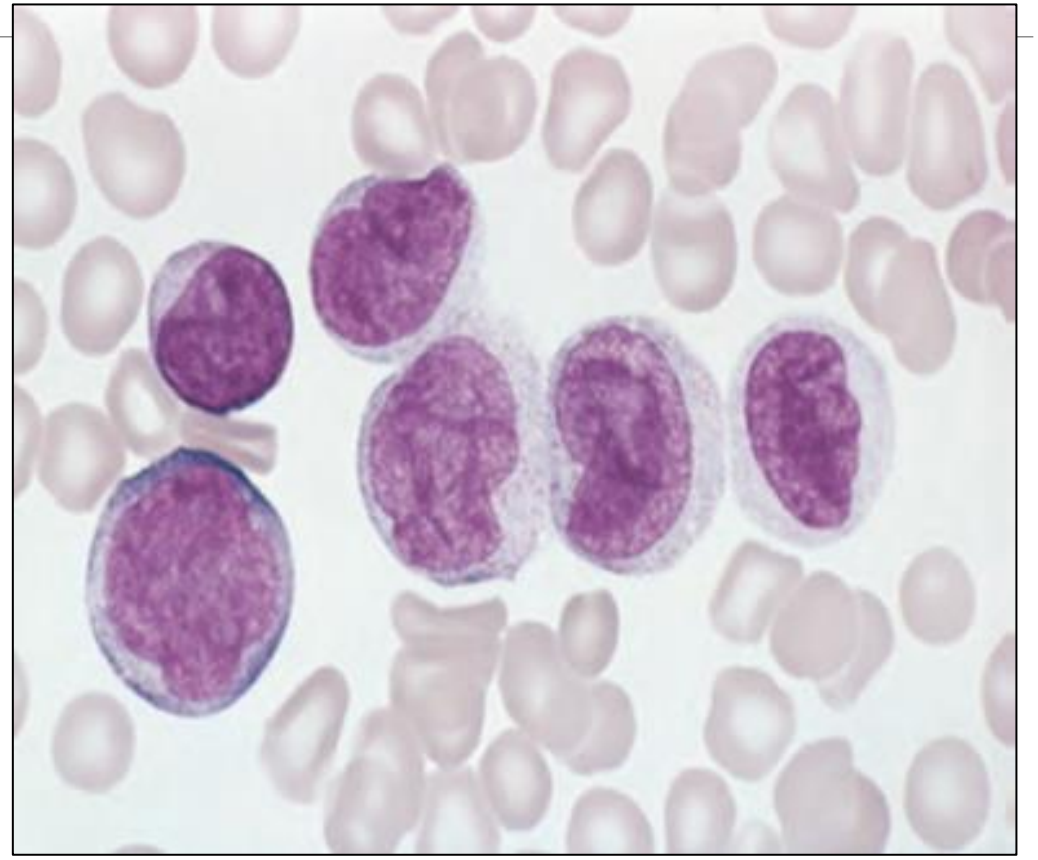
- The neoplastic promyelocytes have abnormally coarse and numerous azurophilic granules.

- A cell in the center of the field with multiple needlelike **Auer rods.**





- Monoblasts have **folded** or lobulated nuclei, **lack Auer rods**



❖ Histochemistry

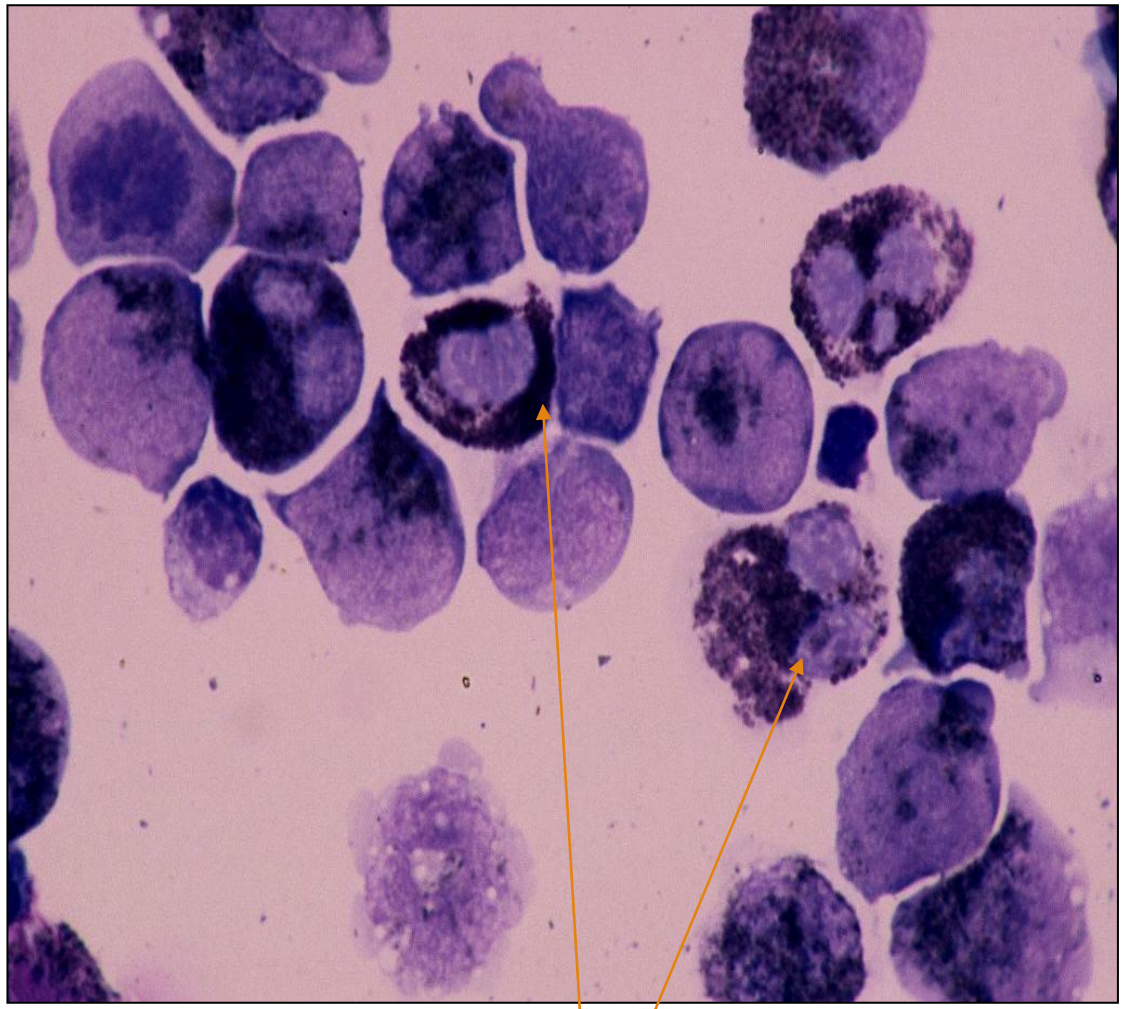
- Cases with granulocytic differentiation are typically positive for the enzyme myeloperoxidase (MPO)

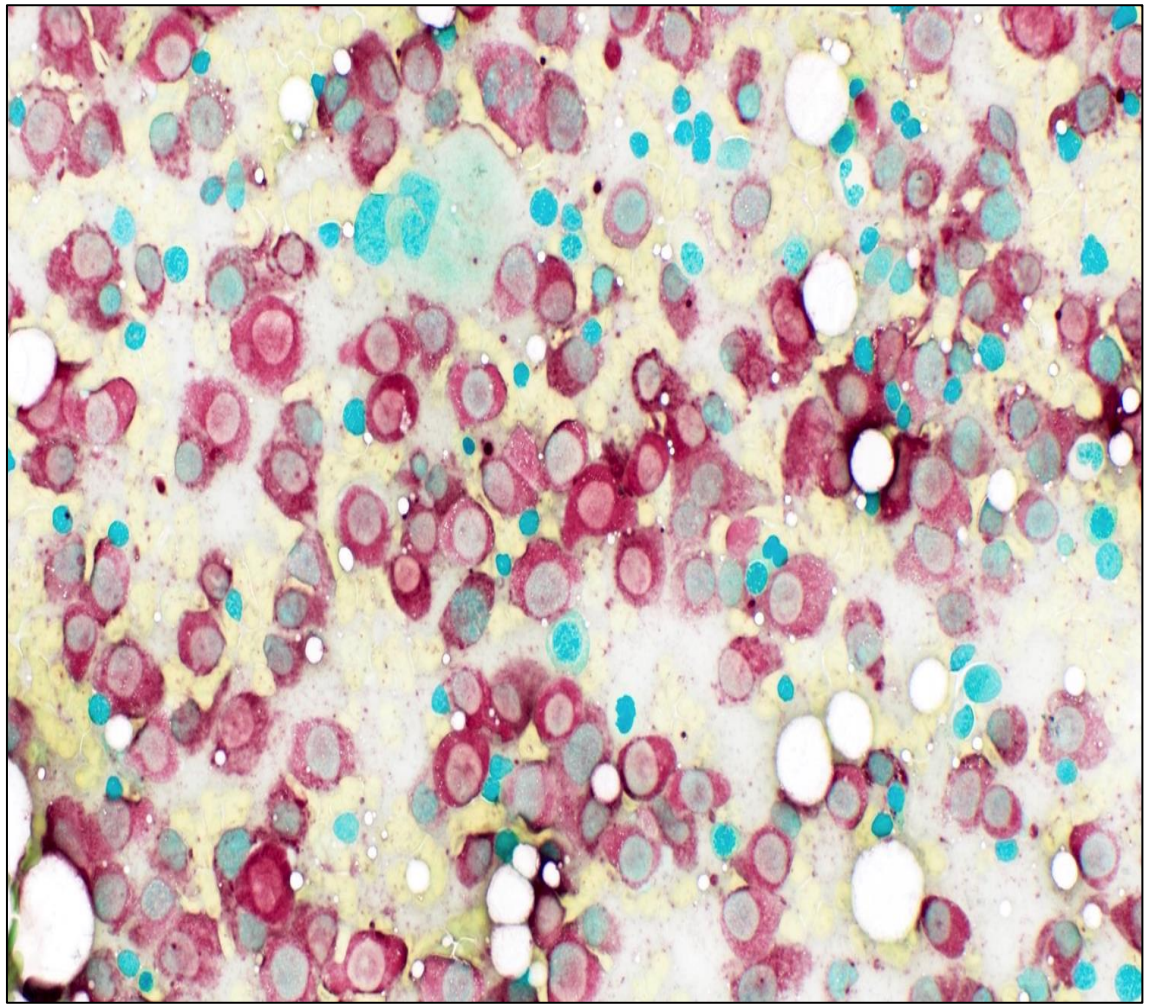
- Monocytic differentiation is demonstrated by staining for lysosomal nonspecific esterase (NSE)

❖ Immunophenotype:

- Positive for myeloid-associated antigens, such as **CD13, CD14**, CD15, CD64, or CD117.

NSE highlights blasts of monocytic origin





❖ Classification

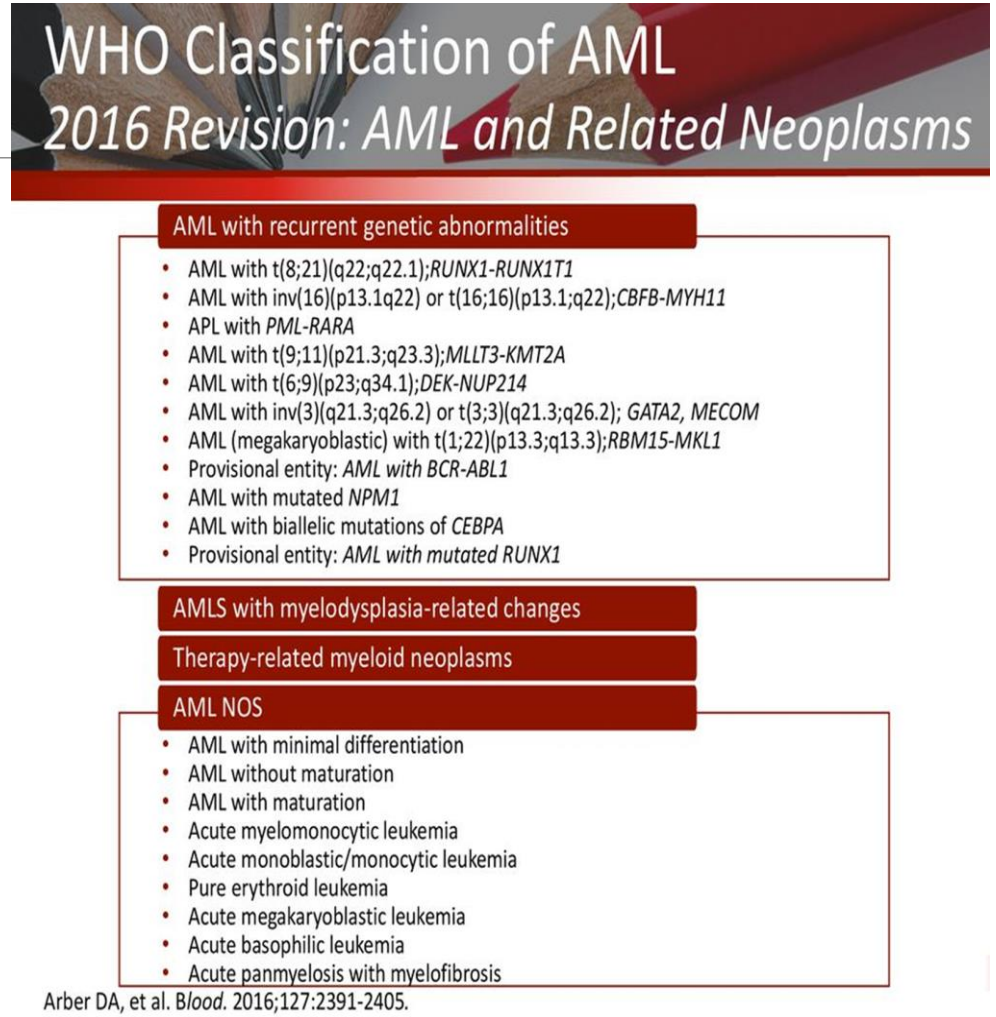
- AMLs are diverse in terms of genetics, cellular lineage, and degree of maturation.
- **The WHO classification relies on these features to divide AML into four categories:**

(1) AMLs associated with specific genetic aberrations

(2) AMLs with dysplasia, many of which arise from MDSs

(3) AMLs occurring after chemotherapy

(4) AMLs lacking any of the foregoing features (subclassified based on the predominant line of differentiation that the tumor exhibits)



Arber DA, et al. Blood. 2016;127:2391-2405.

FAB (French American British) classification of AML

AML-M0 (minimally differentiated) → **>20% blasts**
<3% blasts are MPO +

Myeloid antigens +

No Auer rods

AML-M1 (without maturation) → **>20% blasts**

>3% blasts are MPO+

<10% promyelocytes or mature cells

AML-M2 (with maturation) → **>20% blasts**

>3% blasts are MPO+

>10% promyelocytes or mature cells

<20% monoblasts and promonocytes

AML-M3 (acute promyelocytic leukemia)

>20% blasts and promyelocytes

Intense MPO reactivity

Associated with t(15,17)

High incidence of DIC

AML-M4 (acute myelomonocytic leukemia)

>20% myeloblasts, monoblasts, promonocytes

Monocytic cells range from 20%-80%

Cells stain positive with lysosomal non-specific esterase.

AML-M5 (acute monoblastic and monocytic leukemia)

>20% monoblasts, promoncytes and myeloblasts

>80% monoblastic cells (5A) or monocytic (5B)
No Auer rods

MPO -

AML-M6a (Erythroleukemia)	**>50% are erythroid precursors** **>20% myeloblasts among non-erythroid cells**
AML-M6b (pure erythroid)	**>80% of marrow cells are immature erythroid cells** **No significant myeloblastic component**
AML-M7 (megakaryocytic)	**>20% blasts** **>50% megakaryocytic cells**

AML Course & Prognosis

- Rapidly fatal if untreated.

- With chemotherapy, 70% remission rate and 15-20% 5-year survival.

- **Prognostic Factors**

Patient age

WBC count at presentation

De novo vs. Secondary leukemia

Cytogenetic abnormalities

❖ **Good prognosis**

t(15;17)
t(8,21)
inv(16)

❖ **Poor prognosis**

Age >60 y
Prior MDS (dysplasia)
Therapy-related AML
Leukocytosis >100,000/µL
Early relapse
del 5 or 7
t(9;22)

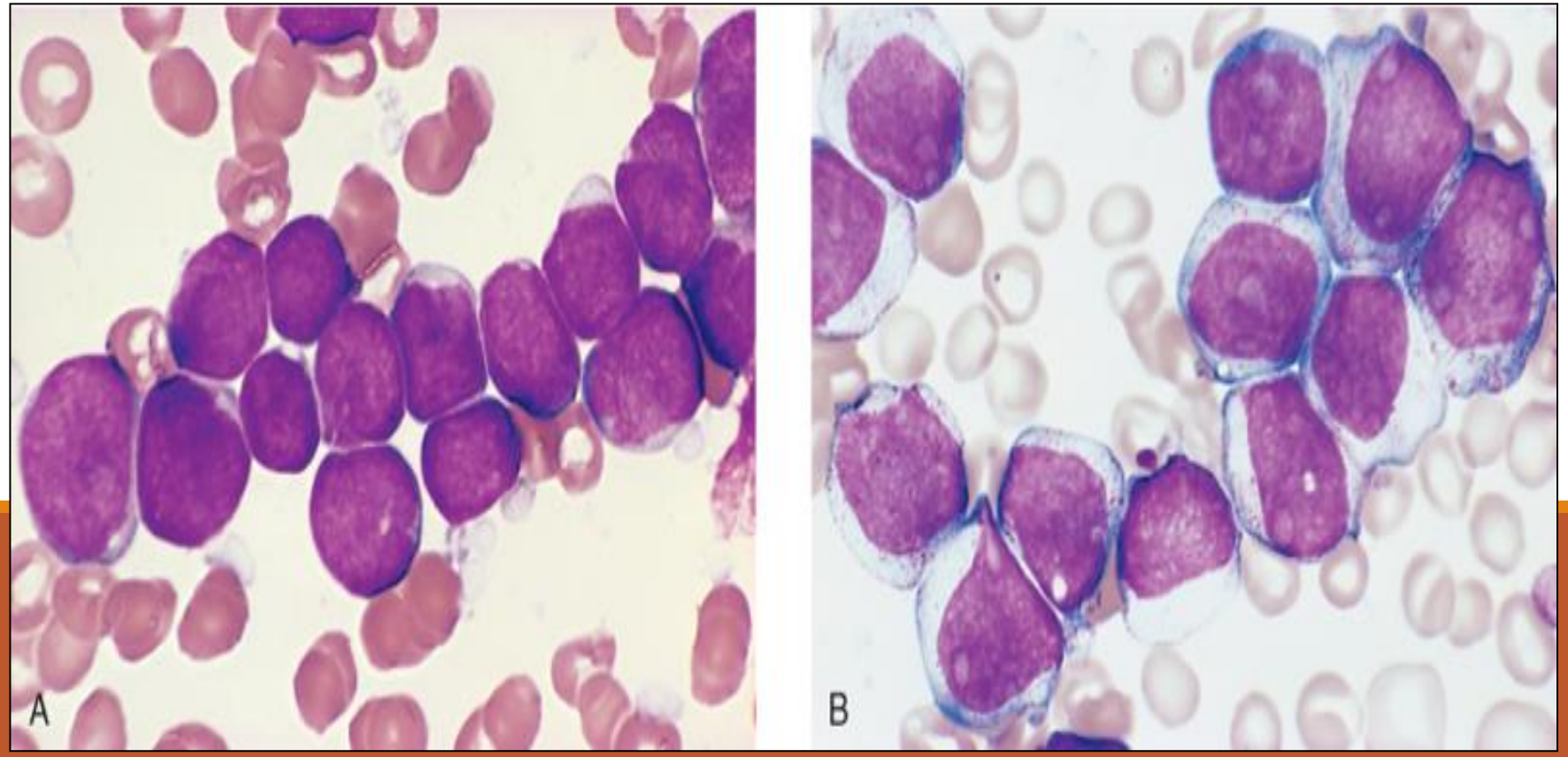
The major differences between AML and ALL

Feature	AML	ALL
Age	Common in adults Rare in children	Common in children Rare in adults
Blood	Myeloblasts	Lymphoblasts
Morphology	Medium to large blasts More cytoplasm Cytoplasmic granules Auer rods Fine chromatin Distinct nucleoli	Small to medium blasts Little cytoplasm No granules (90%) No Auer rods Fine chromatin Indistinct nucleoli
Myeloperoxidase	Positive	Negative
TdT	Negative	Positive
CD Markers	CD13,CD14 CD15,CD33,CD64	CD10,CD19,CD20 CD21,CD23,CD79a

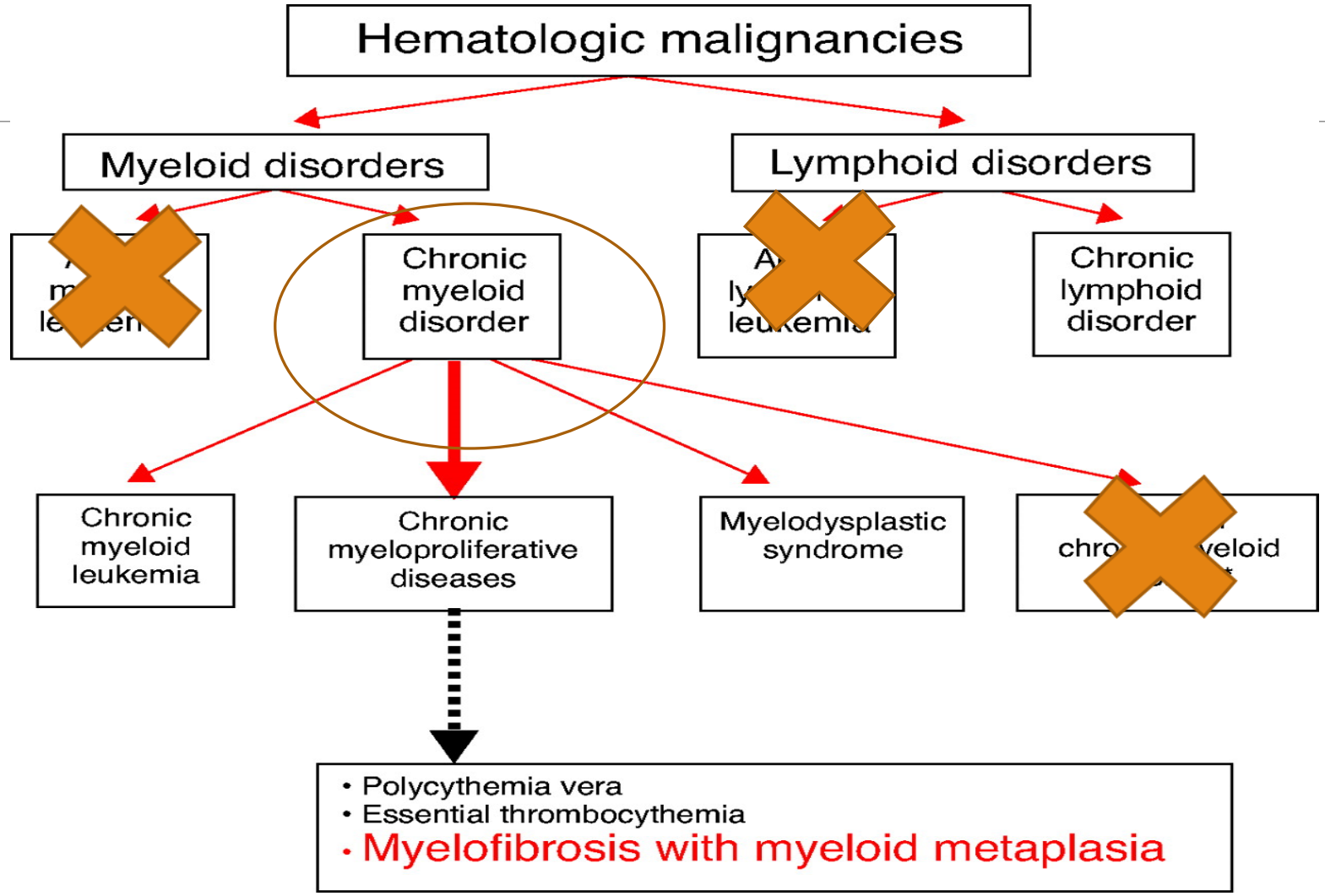
Morphologic comparison of lymphoblasts and myeloblasts.

A. ALL: Lymphoblasts have fewer nucleoli than do myeloblasts, and the nuclear chromatin is more condensed. Cytoplasmic granules are absent.

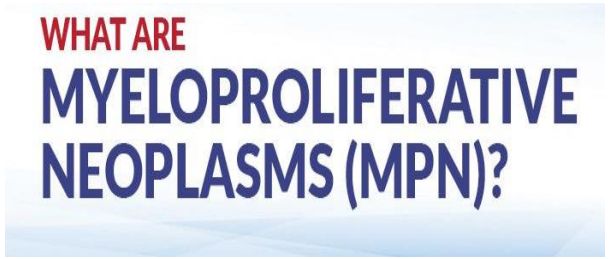
B. AML: Myeloblasts have delicate nuclear chromatin, prominent nucleoli, and fine azurophilic granules in the cytoplasm



Neoplastic Proliferations Of White Cells



Myeloproliferative Neoplasms (MPN)



- A family of acquired malignant clonal disorders of pluripotent stem cells with resulting abnormalities in one or more cell lines.
- At least initially, the clonal stem cells **retain their capacity for terminal differentiation**.
- The hallmark of MPN is the presence of mutated, constituently **active tyrosine kinases** or other acquired aberrations that lead to **growth factor independence.**

- Four major diagnostic entities are recognized

1. Chronic myeloid leukemia (CML)
2. Polycythemia vera
3. Essential thrombocythemia
4. Primary myelofibrosis

○ General characteristics

- Hypercellular marrow with **maturation**
- **Effective** hematopoiesis
- Elevated peripheral blood levels of one or more cell lines:
  - granulocytic (CML)
  - erythroid (polycythemia vera)
  - platelets (essential thrombocythemia)
- Hepatosplenomegaly
- These disorders have many overlapping features.

1. Chronic Myeloid Leukemia (CML)

- A disorder characterized by massive overproduction of normal-appearing but somewhat defective granulocytes.

- Adults between 25 and 60 years (peak in 4^{th}-5^{th} decades).

❑ Differential diagnosis

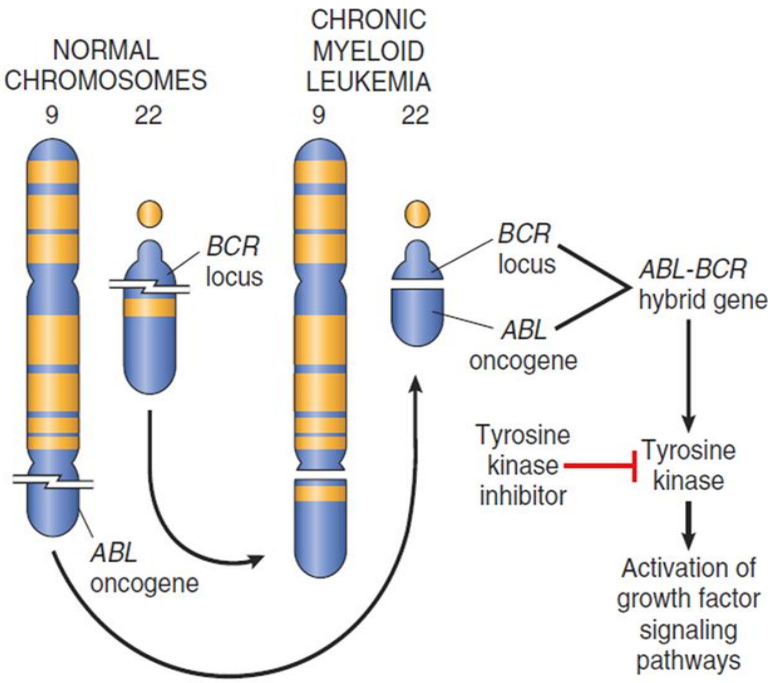
- Leukemoid reaction (a dramatic elevation of the granulocyte count in response to infection, and chronic inflammation),,,,,, Distinction can be achieved by testing for the presence of the BCR-ABL fusion gene.

- Other MPN

Pathogenesis:

- In ~ 95% of cases, there is a **t(9;22) (Philadelphia chromosome)** that *results in* **a chimeric *BCR-ABL* gene which** encodes a fusion protein with **tyrosine kinase activity**.

-The mutation is a stem cell mutation (found in granulocytes, erythroid, megakaryocytes, B and T precursors); however, **the effect is limited to granulocyte and megakaryocyte**.



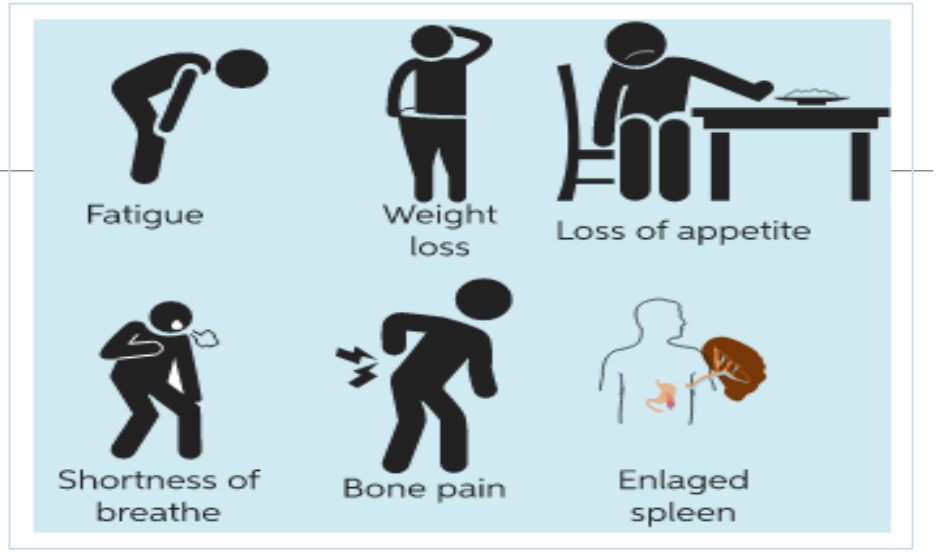
❑ Clinical Features

- Early: patients appear normal

- The onset is insidious.
  - The initial symptoms usually are nonspecific (e.g., anemia with fatigue, weakness, anorexia, weight loss)
  - Bleeding tendencies.
  - Infections.

- Dragging sensation in the abdomen caused by splenomegaly.

- Median survival of **3** years, even without treatment



❑ Laboratory Findings

BP

- The leukocyte count is elevated, often exceeding 100,000 cells/µL.

- The circulating cells are predominantly neutrophils, metamyelocytes, and myelocytes, but basophils and eosinophils are also prominent

– High platelet counts (early), thrombocytopenia (late)

-Mild to moderate anemia

-Low/absent leukocyte alkaline phosphatase (LAP) scores

❑ Pathology

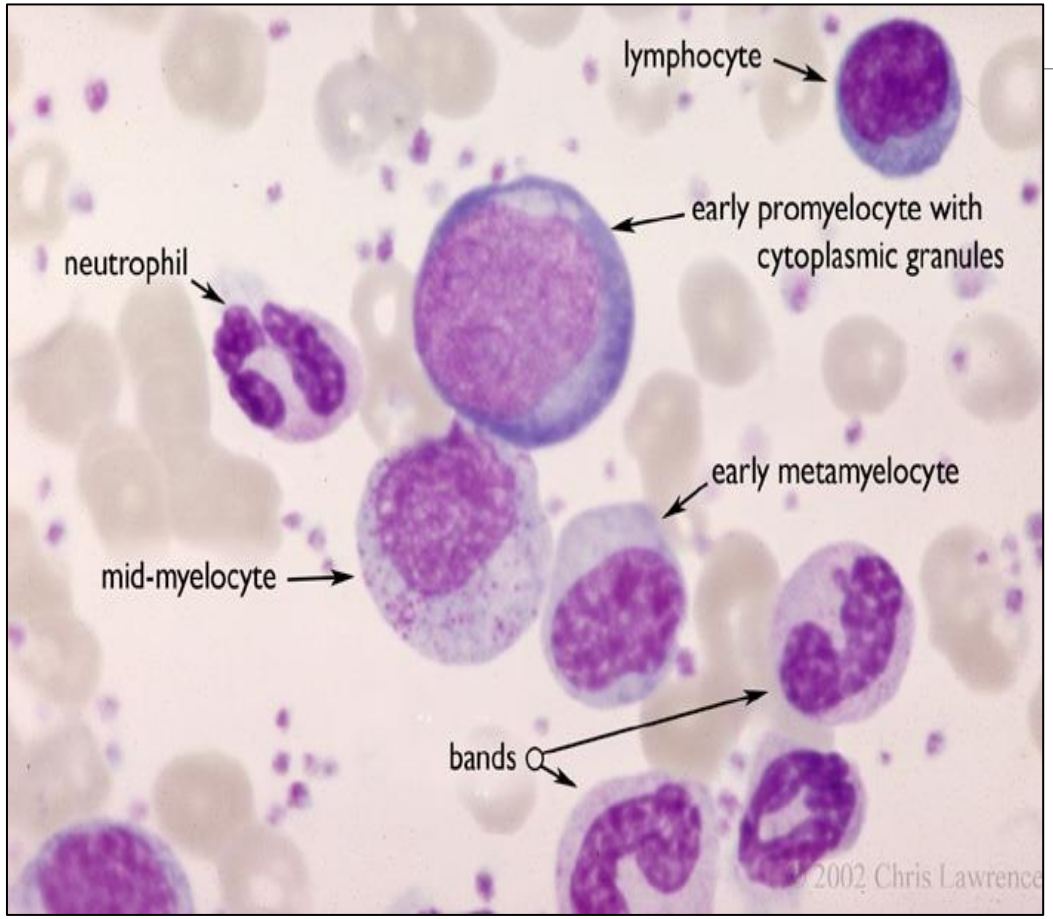
Bone marrow:

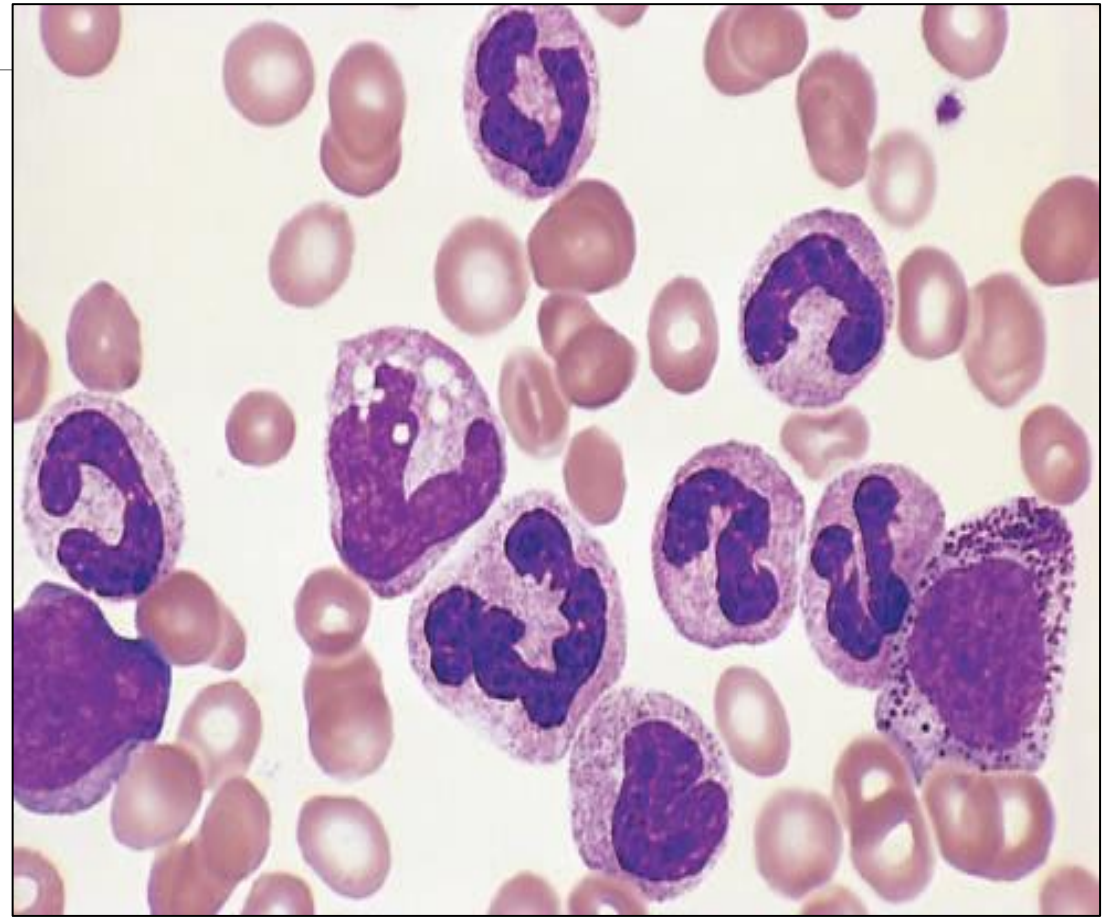
- Markedly hypercellular owing to increased numbers of maturing **granulocytic and megakaryocytic precursors.**
- Mild reticulin fibrosis
- Blasts <10%

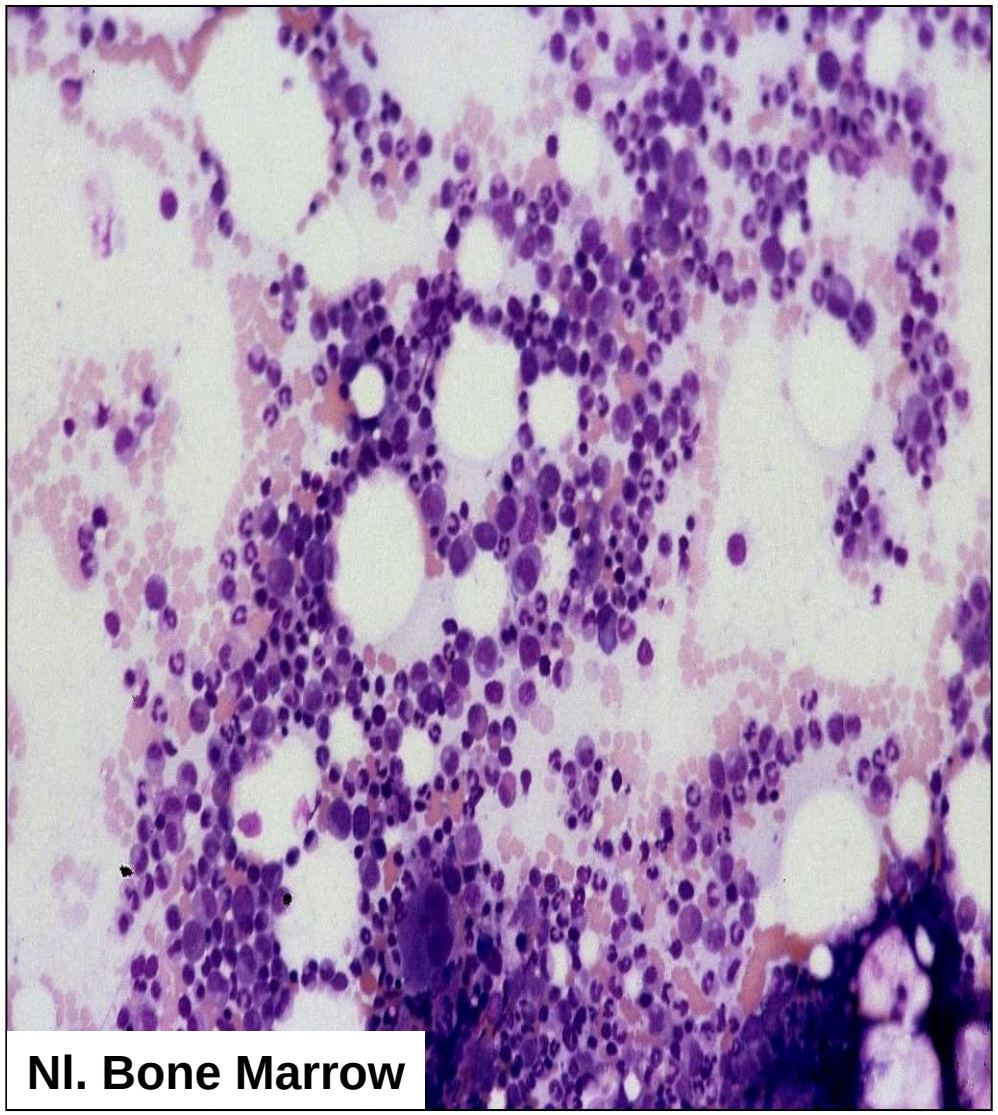
Spleen

- Expanded red pulp with extramedullary hematopoiesis

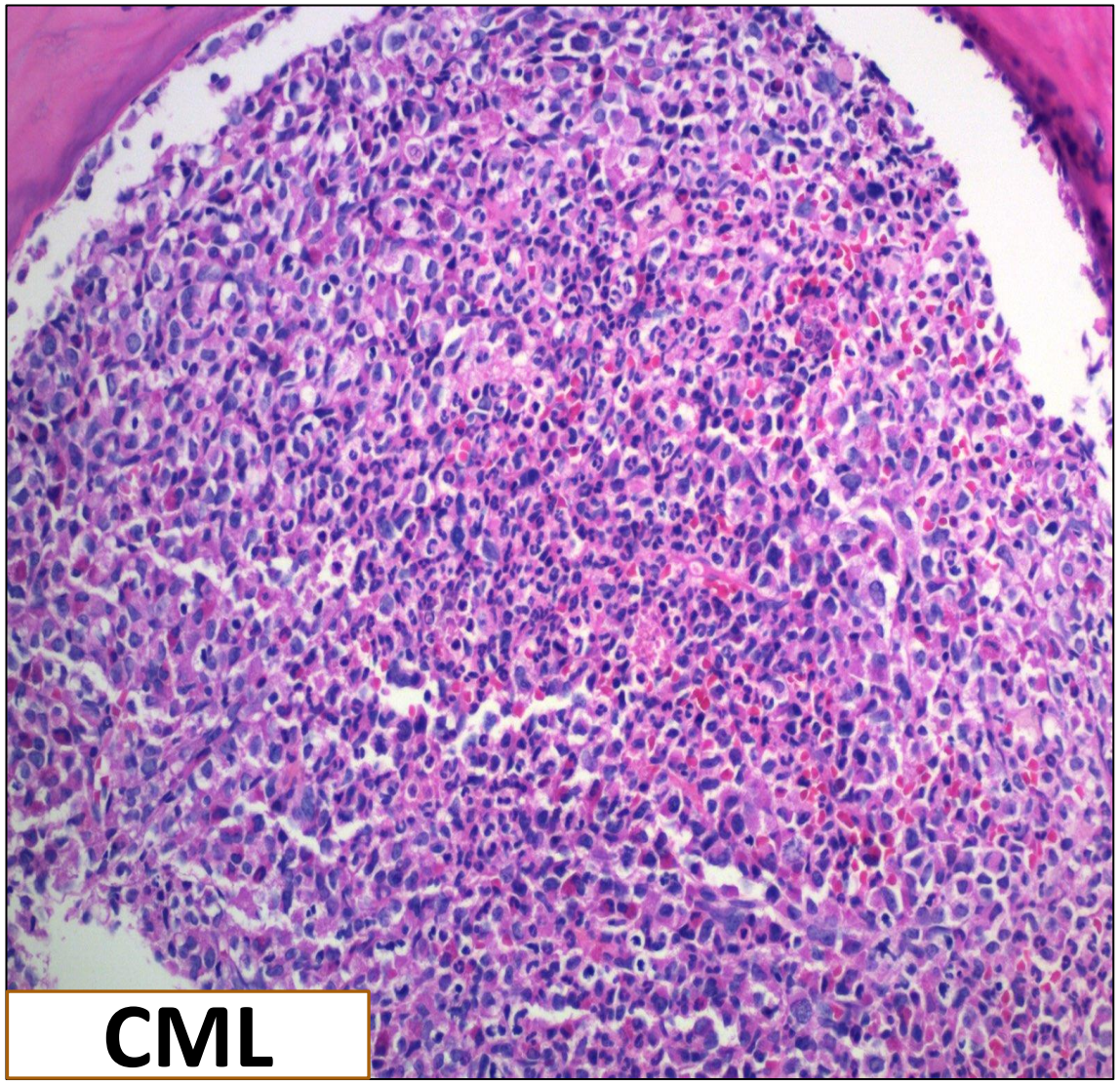
CML—peripheral blood smear: Granulocytic forms at various stages of differentiation are present







Nl. Bone Marrow



CML

❑ Course and Prognosis

- ***Slow progression of 3 phases (chronic, accelerated, and blast crises phases).***

Chronic phase

- 1-5 years
- Mild-moderate elevation of WBC
- Mild anemia
- Blasts <5% in BM
- Organomegaly, which responds to intermittent myelosuppression

Accelerated phase

- 50% of CML cases
- Increase WBC count despite treatment
- Increasing anemia
- New thrombocytopenia
- The appearance of additional cytogenetic abnormalities
- Increasing splenic size despite treatment
- 10 - 19% blasts in BM

Blast crisis

- ≥ 20% blasts (definition of acute leukemia) or extramedullary blast proliferation
- Abrupt or gradual over weeks (**Can occur abruptly without the previous accelerating phase**)
- **70%** are **myeloid** leukemia
- **30%** are **lymphoid** leukemia
- Associated with additional chromosomal abnormalities

Polycythemia

Causes of Polycythemia

- **Relative :** Reduced plasma volume(dehydration due vomiting or diarrhea): Hemoconcentration
- **Absolute:**
  - **Primary**: PV
  - **Secondary**: Increased Erythropoietin level:

- Adaptive: Lung disease, Smoking, cyanotic heart disease, high altitude living
- Paraneoplastic: Erythropoietin secreting tumors: RCC, HCC

2. Polycythemia Vera (PV)

- Insidious clonal disorder of pluripotential hematopoietic stem cells dominated by an expansion of the red cell mass.

- Strongly associated with activating mutations in the **tyrosine kinase JAK2**.

- This produces an excessive proliferation of erythroid, granulocytic, and megakaryocytic elements (**panmyelosis)**.

- But most clinical signs and symptoms are related to an absolute **increase in red cell mass.**

- Associated with **low levels of serum erythropoietin**

	2016 WHO Classification
Major Criteria	1. Hb > 16.5 g/dL in men/Hb > 16.0 g/dL in women, or Hct > 49% in men/Hct > 48% in women, or increased RCM; 2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature, megakaryocytes (differences in size); 3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor Criteria	Subnormal serum EPO level
Criteria required for diagnosis	All 3 major or the first 2 major and the minor criterion

❖ Clinical Findings

- Appears insidiously, in late middle age.

- Manifestations are related to expanded blood volume, increased blood viscosity, and thrombotic and hemorrhagic tendencies (Due to excessive distention of blood vessels and abnormal platelet function):

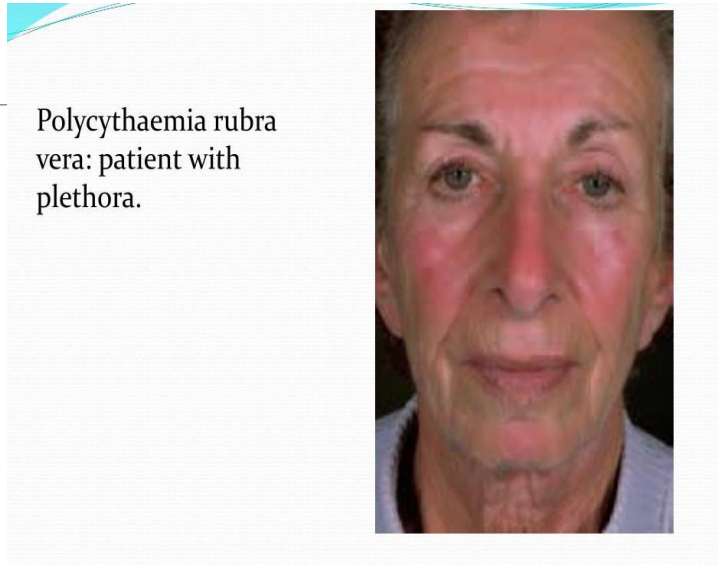
❖Patients are plethoric and somewhat cyanotic.

❖Thrombosis and infarction: Especially heart, spleen, and liver (Hepatic vein thrombosis called Budd-Chiari syndrome).

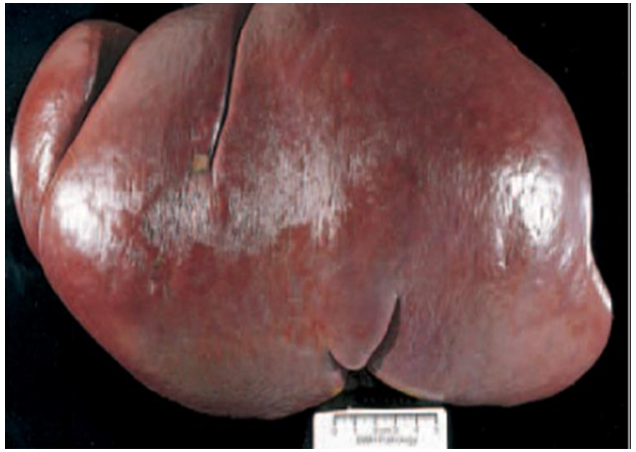
❖Headache, weakness, hypertension, GIT Sx, hematemesis, and melena are common

❖Pruritus.

❖Splenomegaly



Polycythaemia rubra vera: patient with plethora.



❖ Laboratory Findings

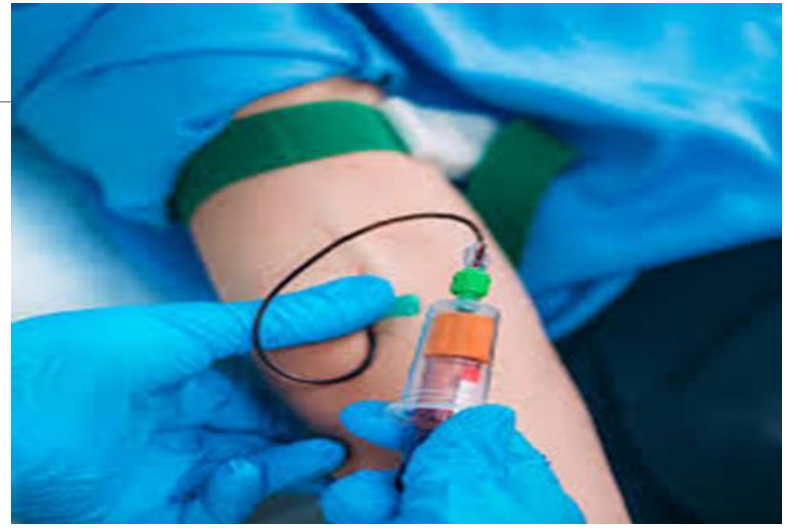
- High red cell counts.
- High hematocrit
- High granulocyte count
- High platelet count (The platelets are functionally abnormal in most cases, and giant platelets and megakaryocyte fragments are often seen in the blood)
- Basophilia is common.

❖ Pathology

Bone marrow:

- Hypercellular owing to increased numbers of erythroid, myeloid, and megakaryocytic forms.
- Some degree of marrow fibrosis.
- Splenomegaly and enlarged liver
- Organs thromboses and infarctions

❖ **PV** Course & Prognosis



- **Proliferative phase**
  Erythroid proliferation
  Median survival –10 years (With repeated phlebotomy)
- **Spent phase**: 15-20% (marrow fibrosis)
- **AML**: 5-10%

- Without treatment, death occurs from vascular complications within months.
- With treatment, the median survival is increased.

3. Essential Thrombocythemia (ET)

- **A clonal stem cell disorder characterized by elevated platelet counts** and fulfills all 4 WHO criteria:

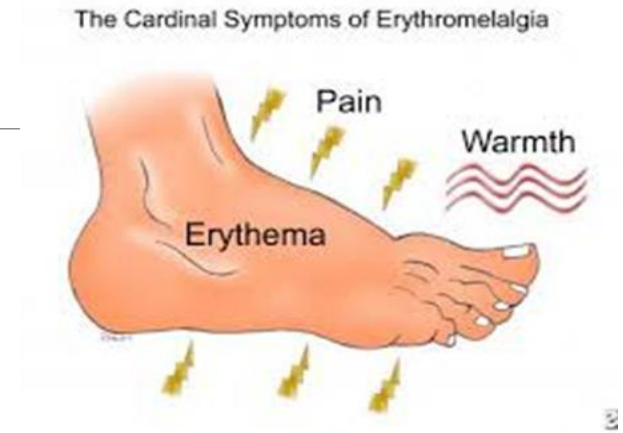
1. Sustained Platelet count > 450,000 /µl
2. Hyperplasia of large mature marrow megakaryocytes with no significant granulopoiesis or erythropoiesis.
3. Not meeting WHO criteria for PV, PMF, BCR-ABL1+CML or MDS, or other Myeloid Neoplasms
4. JAK2, MPL or another clonal marker, if not: absence of known causes of reactive thrombocytosis.

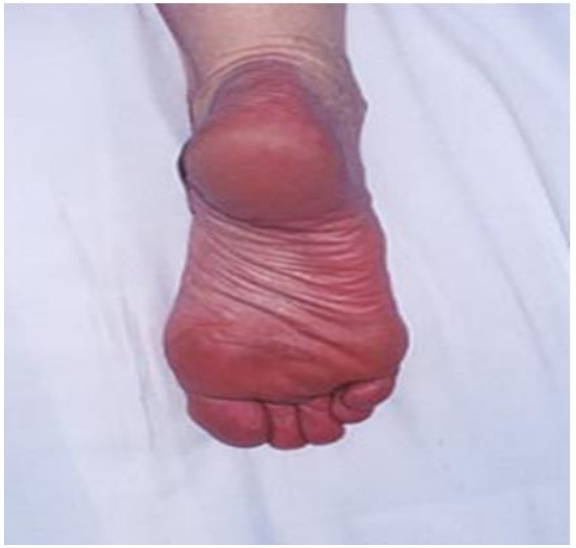
❑ Clinical Findings

- Usually, > 60 yrs.

- No symptoms early in the clinical course.

- Hemorrhage or thrombotic episodes.
  - Recurrent gastrointestinal bleeding and epistaxis are common.
  - Venous or arterial thrombosis.
  - Throbbing and burning in palms, soles, and toes (erythromelalgia).
  - Iron deficiency due to recurrent bleeding episodes.
  - Splenomegaly.
  - Acute leukemia 10% of patients



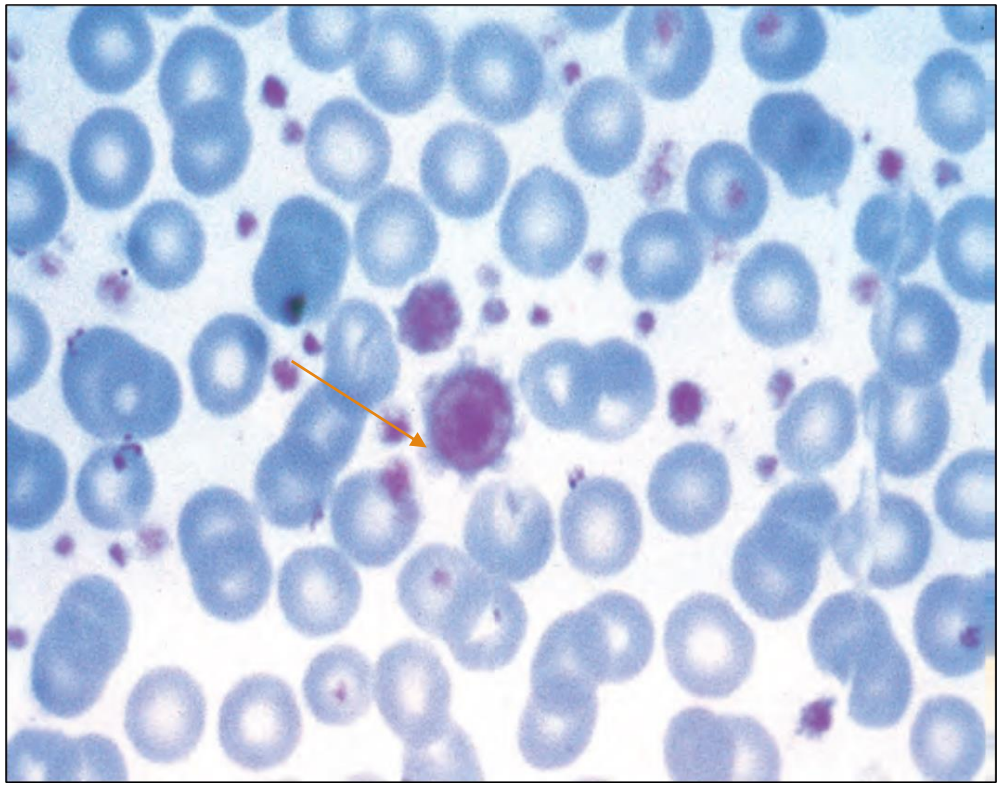


❑ Pathology:

Peripheral blood smear shows marked thrombocytosis, including giant platelets approximating the size of surrounding red cells.

❑ **Bone marrow:**

- Cellularity is usually only mildly increased, but megakaryocytes are often markedly increased in number and include abnormally large forms (hyper lobulated nuclei (staghorn nuclear appearance).

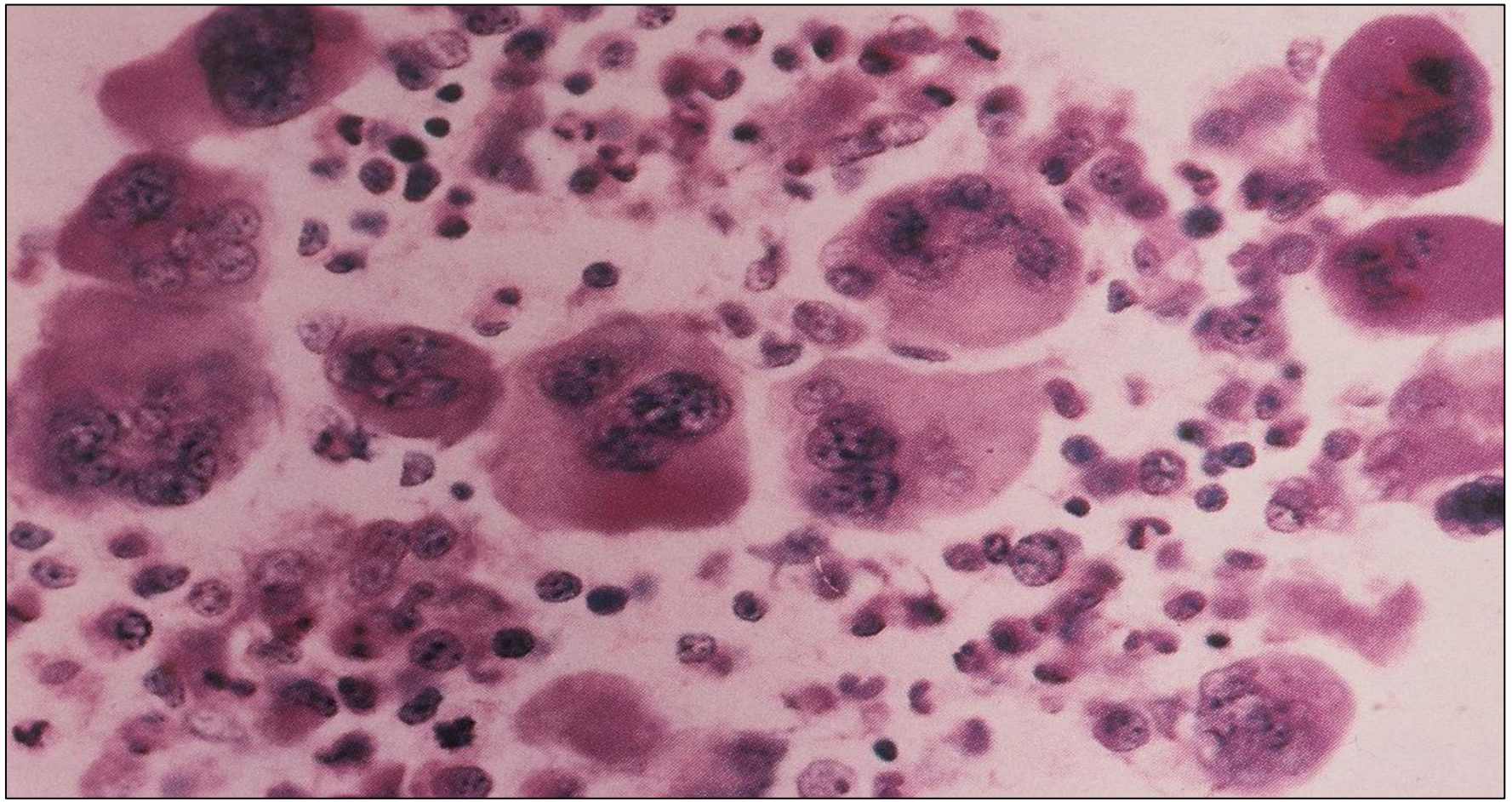


❑ **Peripheral smears**

- Usually reveal abnormally large platelets

❑ Modest degrees of extramedullary hematopoiesis may occur, producing mild organomegaly.

Essential Thrombocythemia (ET)



4. Primary Myelofibrosis

A chronic myeloproliferative disorder characterized by:

- Bone marrow fibrosis
- Leukoerythroblastosis
- Splenomegaly and extramedullary hematopoiesis

- Fibroblast proliferation stimulated by platelet-derived growth factor(PDGF)and transforming growth factor β (TGF β) released from neoplastic megakaryocytes.

❑ WHO Criteria: overt fibrotic stage, all 3 major and at least 1 minor for Dx

Major:

1. Megakaryocytes proliferation+ fibrosis
2. Not meeting PV, CML, MDS, or MN by WHO criteria
3. JAK2 or other clonal but if not: no evidence of reactive fibrosis

Minor:

1. Leukoerythroblastosis
2. Increase in LDH
3. Anemia
4. splenomegaly
5. Leukocytosis

The median survival is in the range of 4 to 5 years.

❑ Clinical Findings

- Usually, > 60 yrs.

- Progressive anemia and splenomegaly.

- Fatigue, weight loss, and night sweats are common.

- Hyperuricemia and secondary gout resulting from a high rate of cell turnover are also frequent.

- # Morphology

- Peripheral blood:

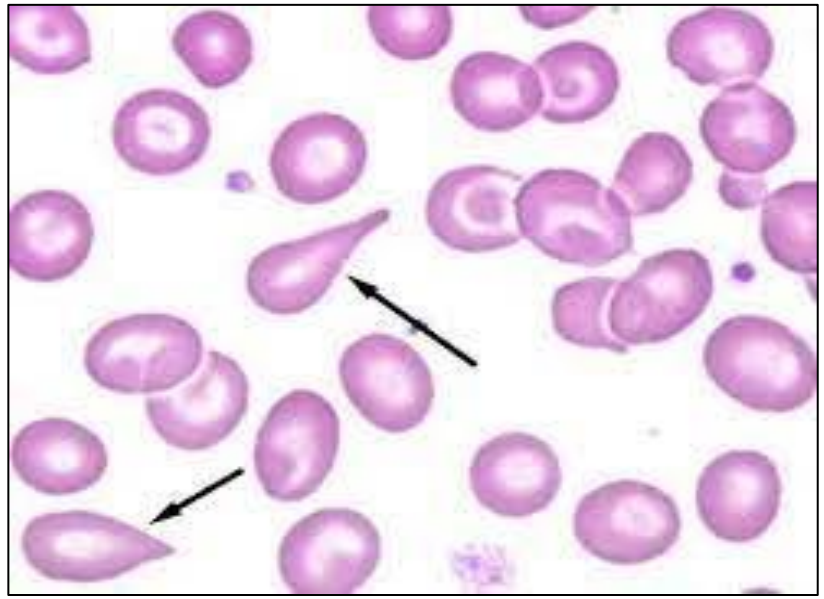
- Anemia with progressive worsening. Teardrop cells
- WBC count: Elevated (early), normal or reduced
- PLt: Normal or elevated (Early), decreased (Late)
- **Leukoerythroblastosis** (Red cells exhibit bizarre shapes **(poikilocytes, teardrop cells)**, and nucleated erythroid precursors along with immature white cells (myelocytes and metamyelocytes)).
- Abnormally large platelets

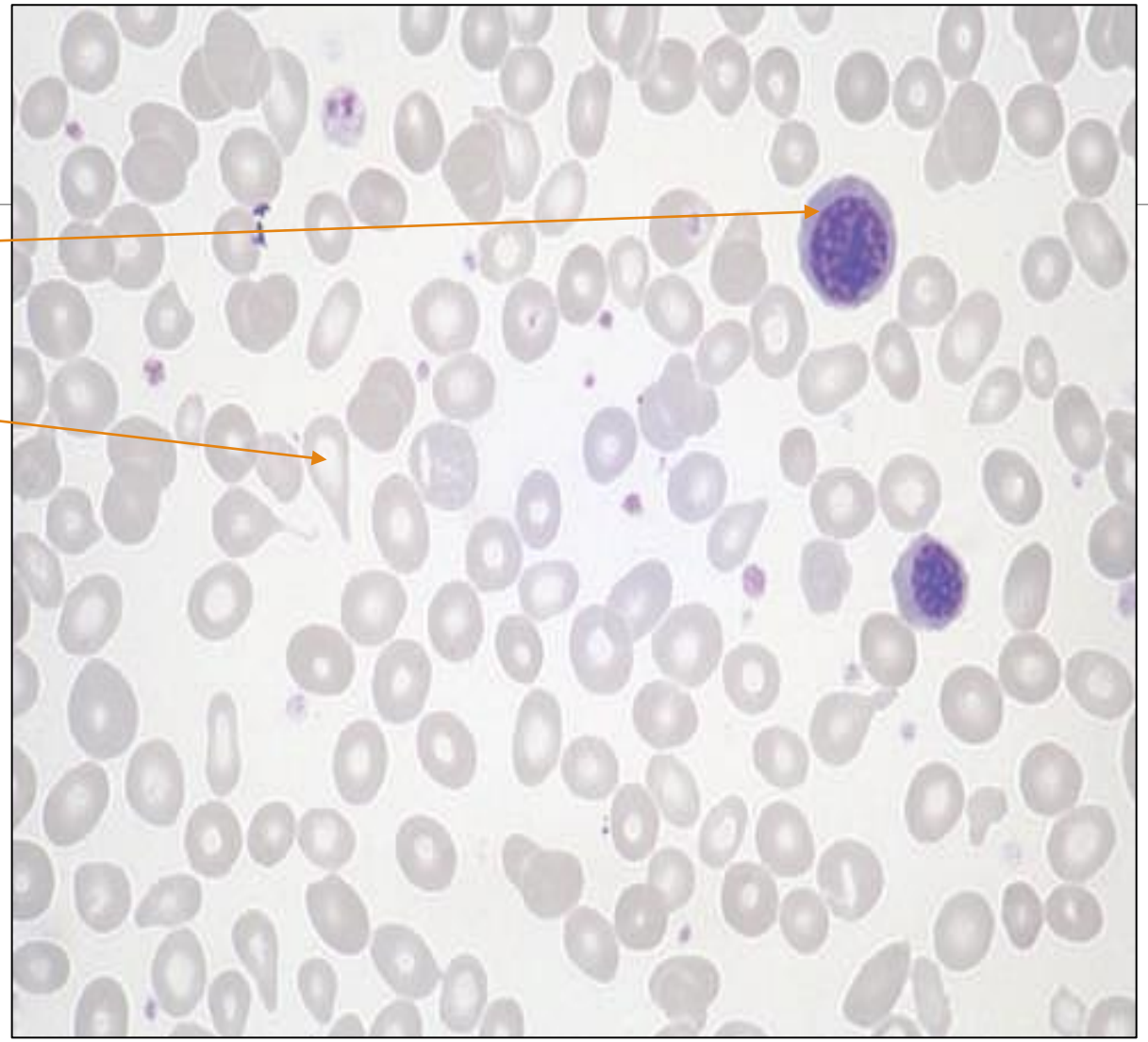
- Bone marrow:

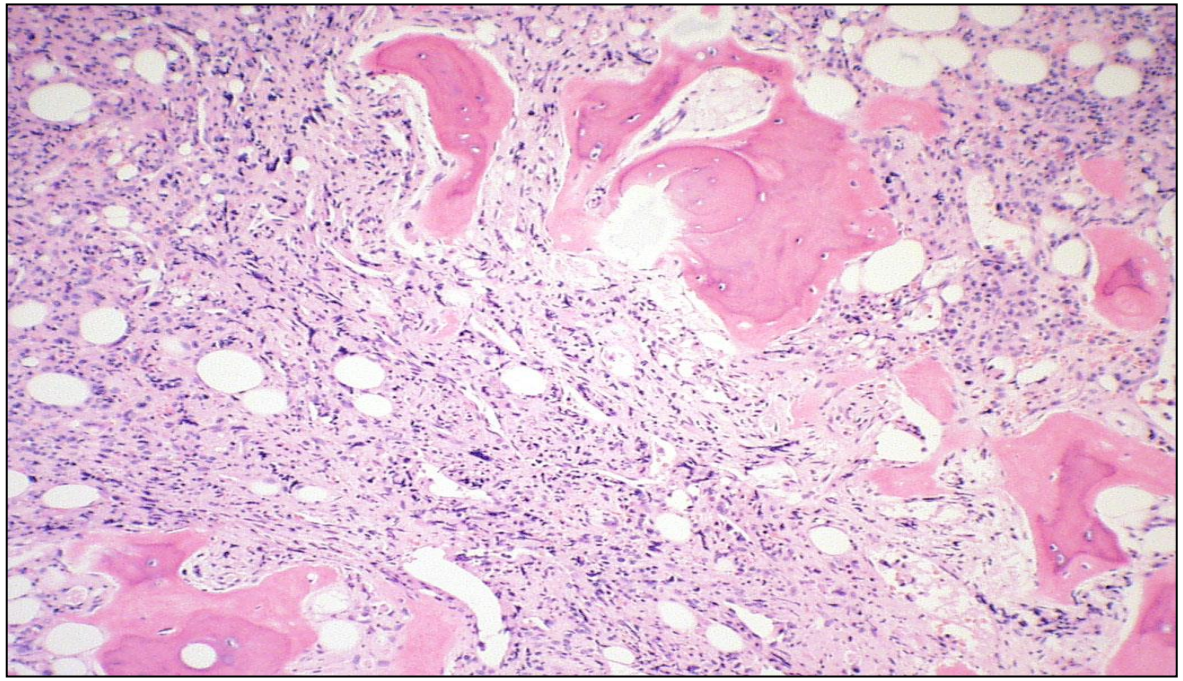
- Hypercellular (Early), Hypocellular, and diffusely fibrotic (Advanced)
- Bone marrow aspiration usually results in a "dry" tap.
- Throughout the course, marrow megakaryocytes are present in clusters and have characteristic **hyperchromatic nuclei with “cloudlike” outlines**.

Primary myelofibrosis—peripheral blood smear.

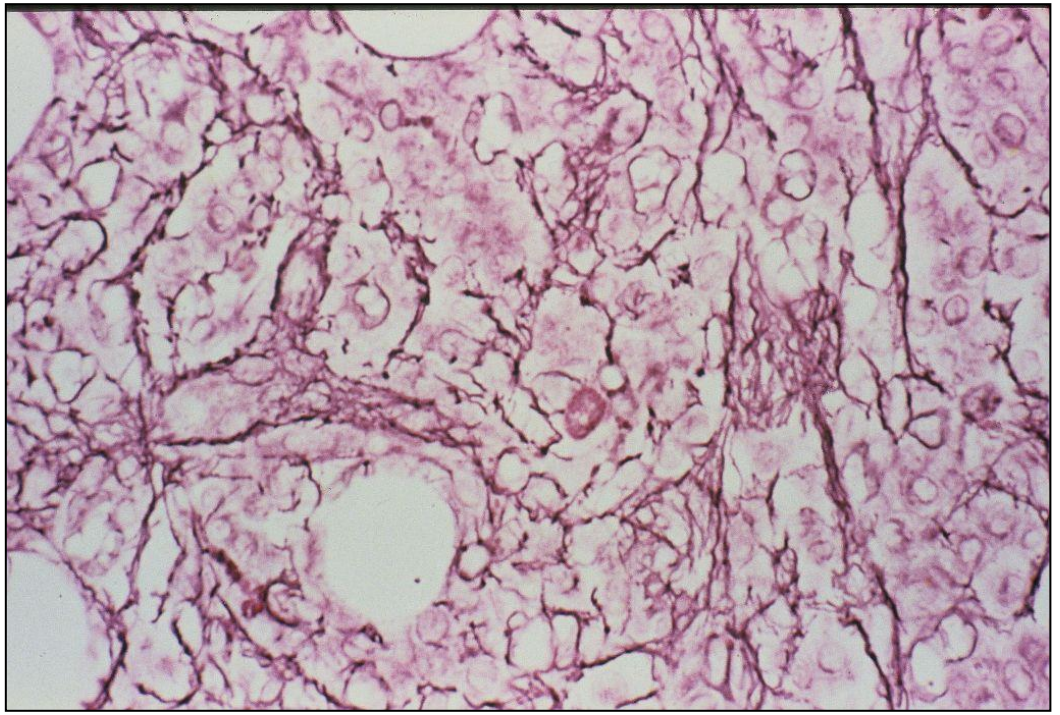
-Two nucleated erythroid precursors and several teardrop-shaped red cells are evident.



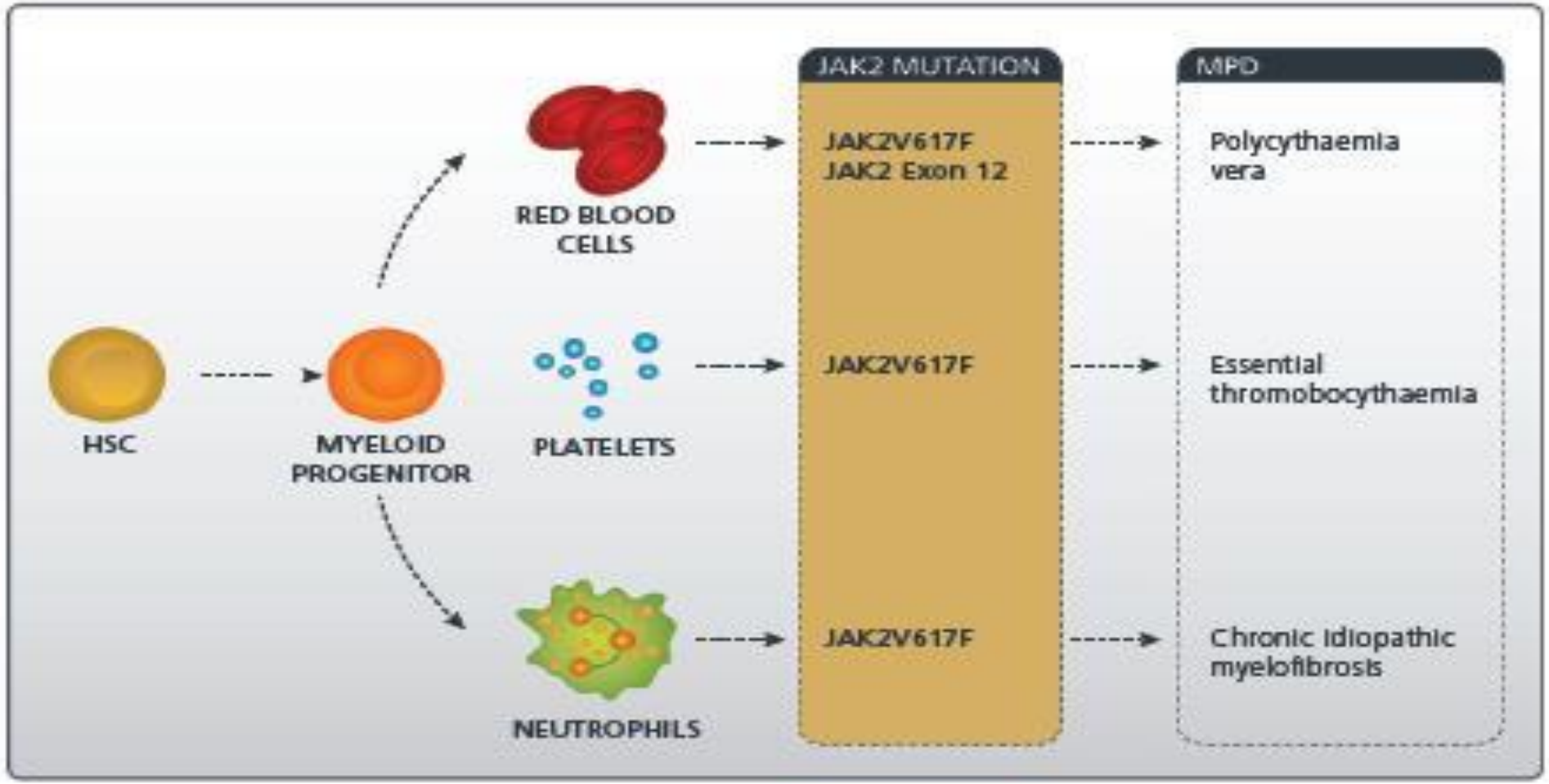




Reticulin Fibrosis



JAK2 Mutations in MPN



95%

50%

50%

Myelodysplastic Syndromes (MDS)

Clonal disorders of hematopoietic stem cells characterized by maturation defects and:

- **In**effective hematopoiesis (bone marrow failure).
  - **hyper**cellular bone marrow.
  - Peripheral pancytopenia.
- Morphologic abnormalities (dysplasia) of peripheral blood and bone marrow cell
- A tendency to develop acute myeloid leukemia.

- Idiopathic or secondary to radiation and alkylating chemotherapy

❖ Pathogenesis

- Mutations in transcription factors

- Frequent mutations in factors that regulate DNA methylation.

- May have mutations in TP53.

- Recurrent chromosomal abnormalities, including deletions of 5q, 7q, and 20q, and trisomy 8.

Clinical Features and prognosis:

- Presents between the ages of 50 and 70 yrs

- Infections, symptoms related to anemia or hemorrhage.

- **Response to conventional chemotherapy is poor**

- Prognosis variable: the median survival time ranges from 9 to 29 months

WHO (2016) Classification for MDS
MDS with single lineage dysplasia (MDS-SLD)
MDS with multilineage dysplasia (MDS-MLD)
MDS with ringed sideroblasts and single lineage dysplasia (MDS-RSSLD)
MDS with ringed sideroblasts and multilineage dysplasia (MDS-RSMLD)
MDS with excess blasts-1 (MDS-EB1)
MDS with excess blasts-2 (MDS-EB2)
MDS, unclassified
MDS indicates myelodysplastic syndromes; WHO, World Health Organization. Adapted from Arber DA, et al.[39]

❖ Morphology

The marrow is populated by abnormal-appearing hematopoietic precursors. Some of the more common abnormalities include:

- Megaloblastoid erythroid precursors resembling those seen in the megaloblastic anemias.
- Erythroid forms with iron deposits within their mitochondria (**ring sideroblasts**)
- Granulocyte precursors with abnormal granules or nuclear maturation (Hyposegmented and occasionally hypersegmented neutrophils
- Small megakaryocytes (Micromegakaryocytes) with single small nuclei or multiple separate nuclei.

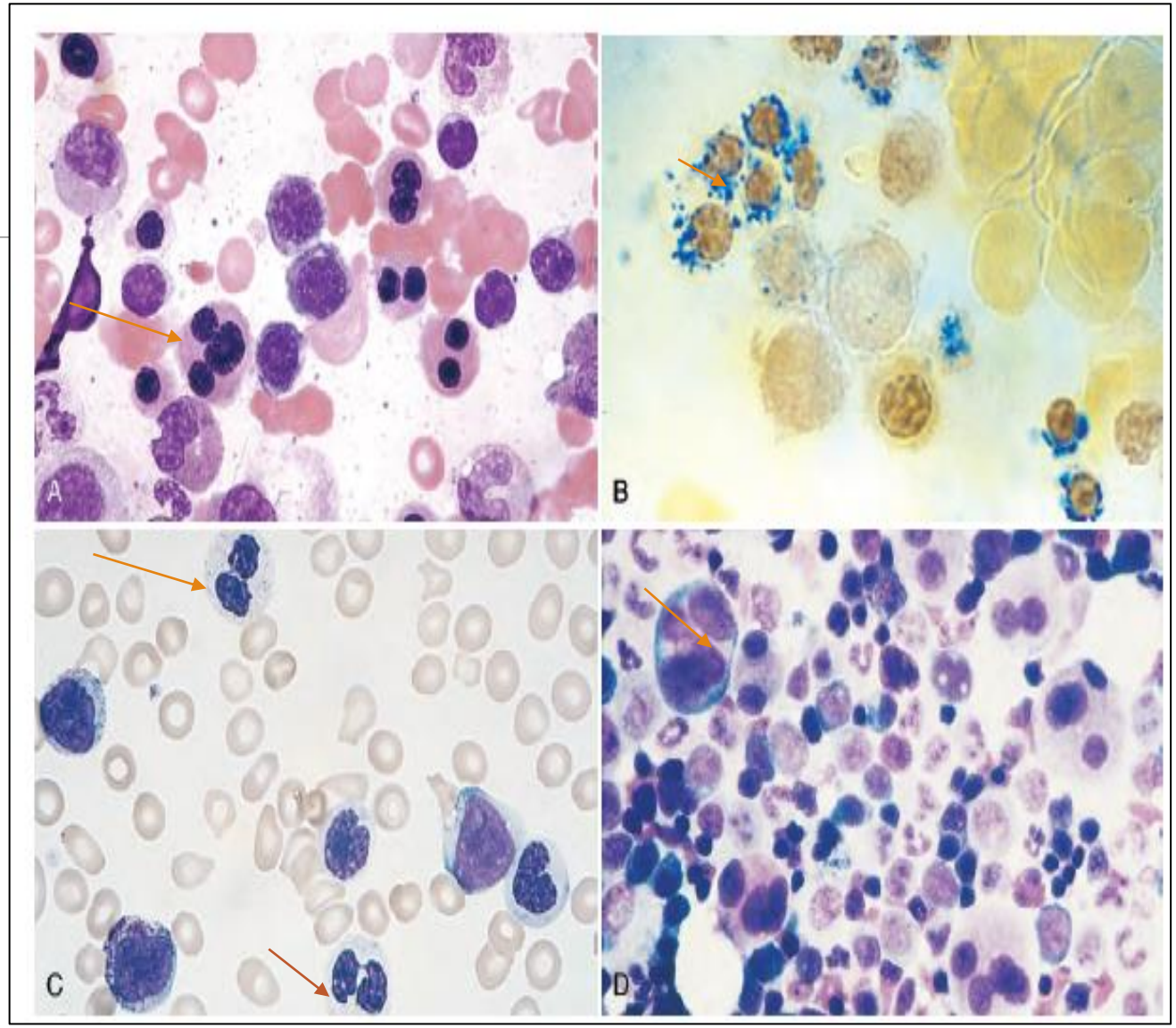
Myelodysplasia. Characteristic forms of dysplasia are shown (**A, B, D,** Marrow aspirates; **C,** peripheral blood smear.)

A, Nucleated red cell progenitors with multilobated or multiple nuclei.

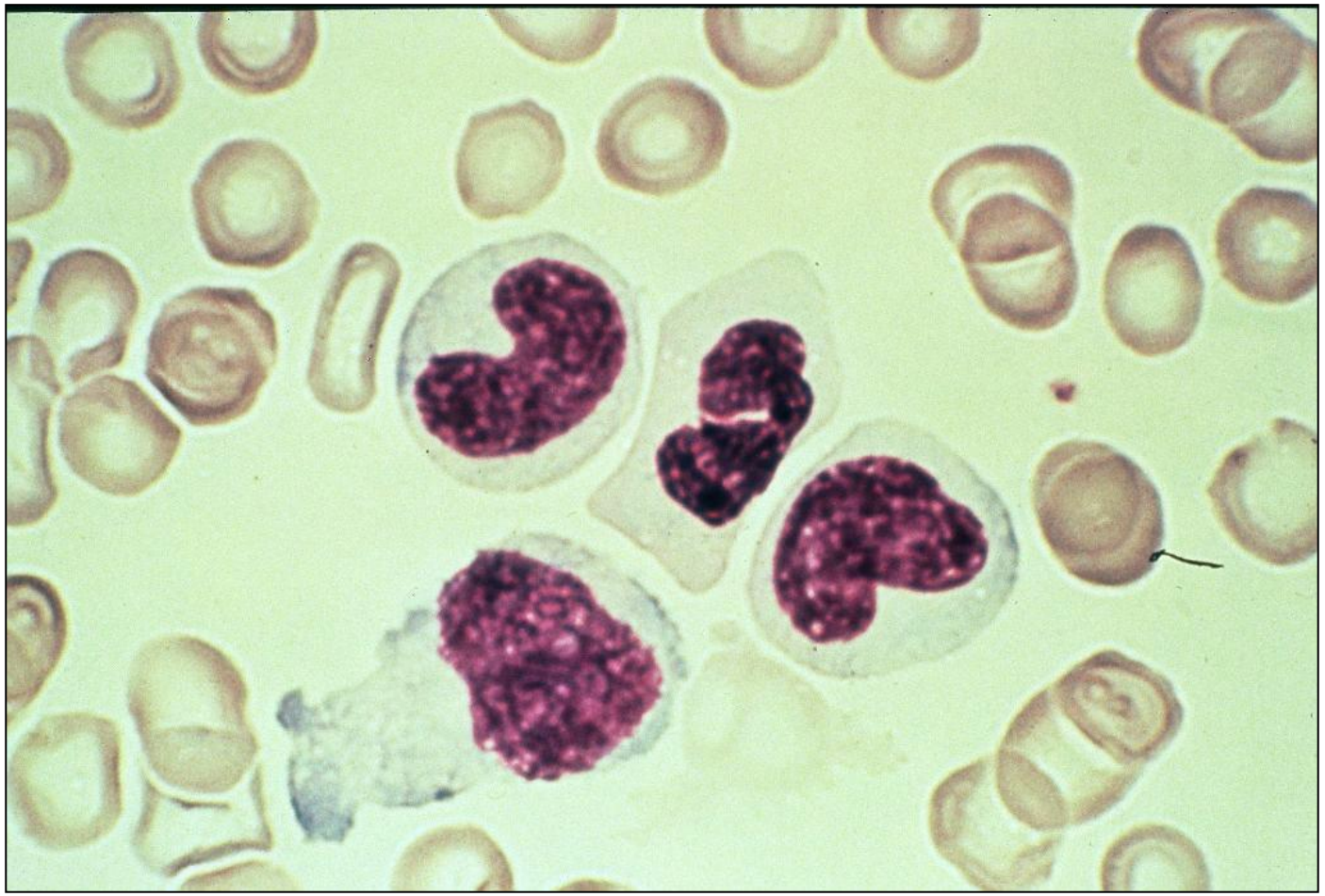
B, Ringed sideroblasts, erythroid progenitors with iron-laden mitochondria seen as blue perinuclear granules (Prussian blue stain).

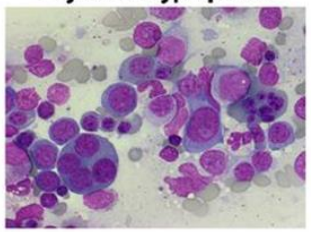
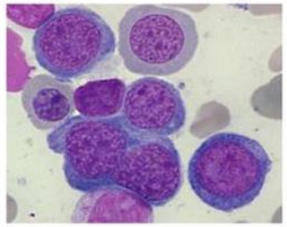
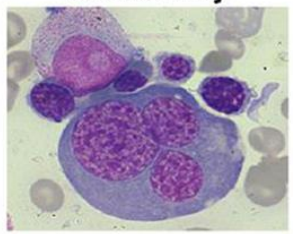
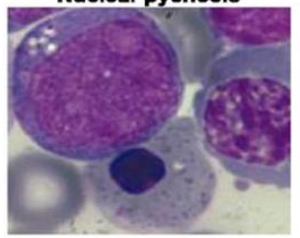
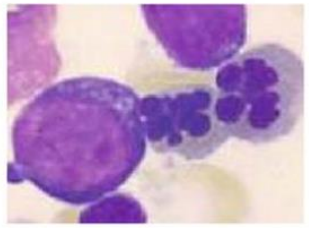
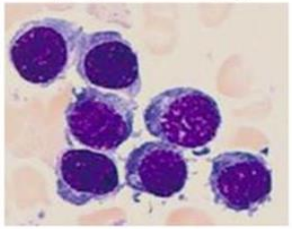
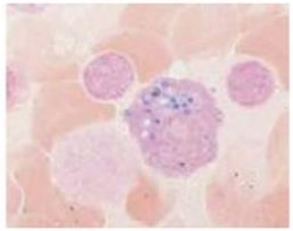
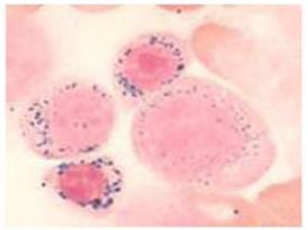
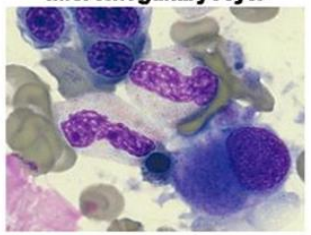
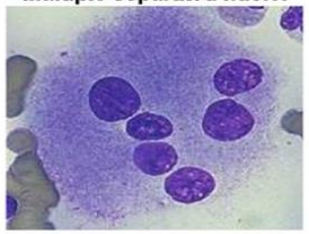
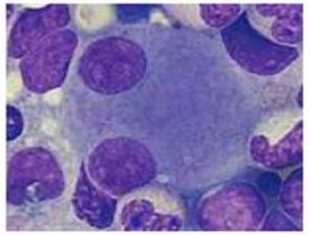
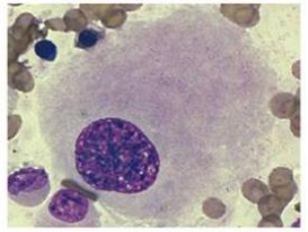
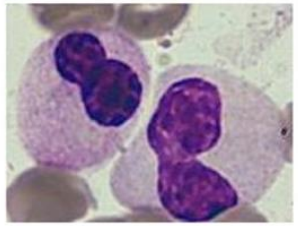
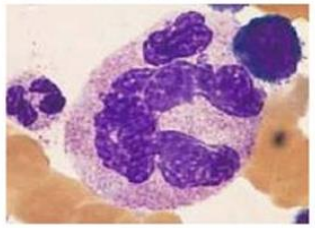
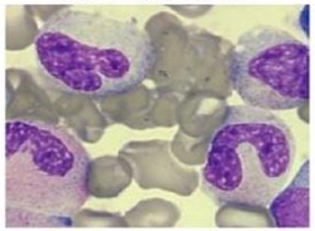
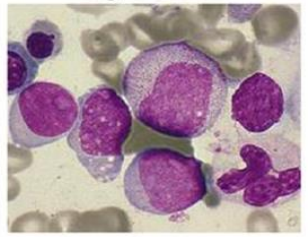
C, Neutrophils with only two nuclear lobes instead of the normal three to four

D, Megakaryocytes with multiple nuclei instead of the normal single multilobated nucleus.



Hpogranular Myeloid Cells



Erythroid lineage	Erythroid hyperplasia 	Megaloblastoid changes 	Multinuclearity 	Nuclear pycnosis 
	Nuclear lobulation 	Cytoplasmic fraying 	Ferritin sideroblast 	Ring sideroblasts 
Megakaryocyte lineage	Micromegakaryocyte 	Multiple separated nuclei 	Small binucleated cell 	Monolobar cell 
Granulocytic lineage	Pseudo-Pelger anomaly 	Abnormal nuclear shape 	Hypo-degranulation 	Myeloblasts 

Thank you