

Disorders of WBCs and lymph nodes

Dr. Hind Al-Sarayrah
M.D
Histopathology specialist

Introduction

❖ The components of the hematopoietic system divided into:

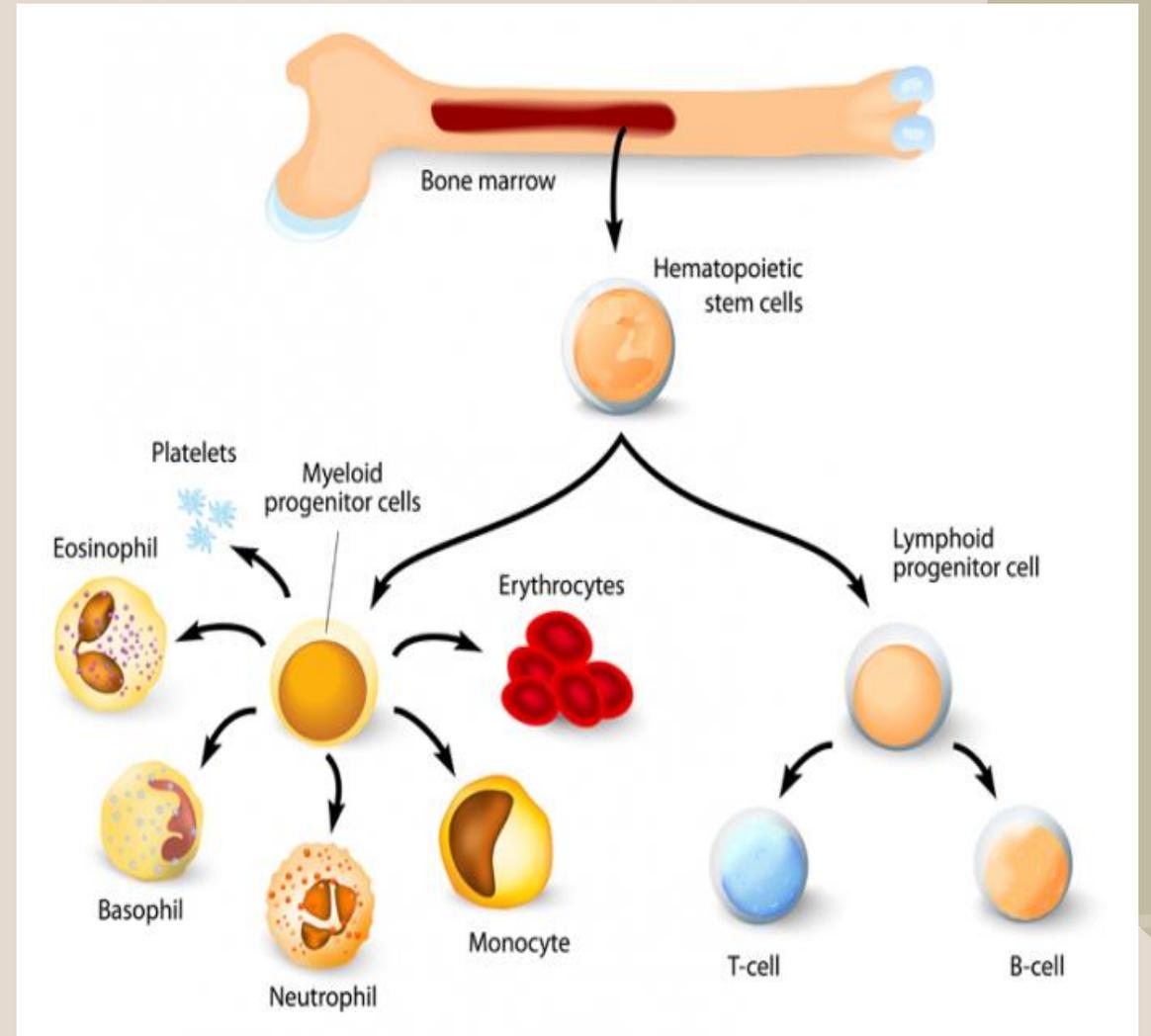
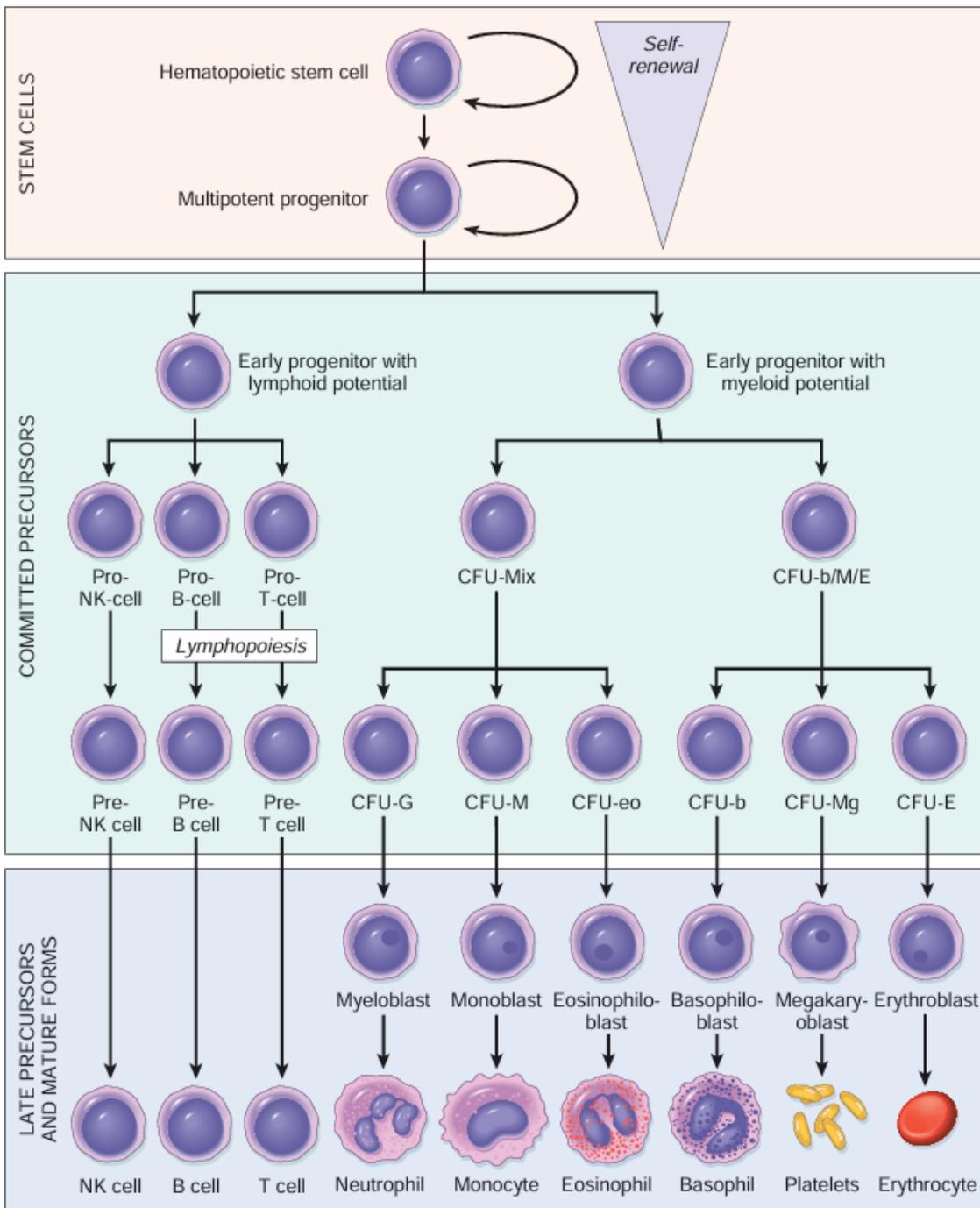
- 1) the **myeloid tissues**, which include the bone marrow and the cells derived from it (e.g., red cells, platelets, WBCs).
- 2) **lymphoid tissues**, consisting of the thymus, lymph nodes, and spleen

• Disorders of white blood cells can be classified into two broad categories:

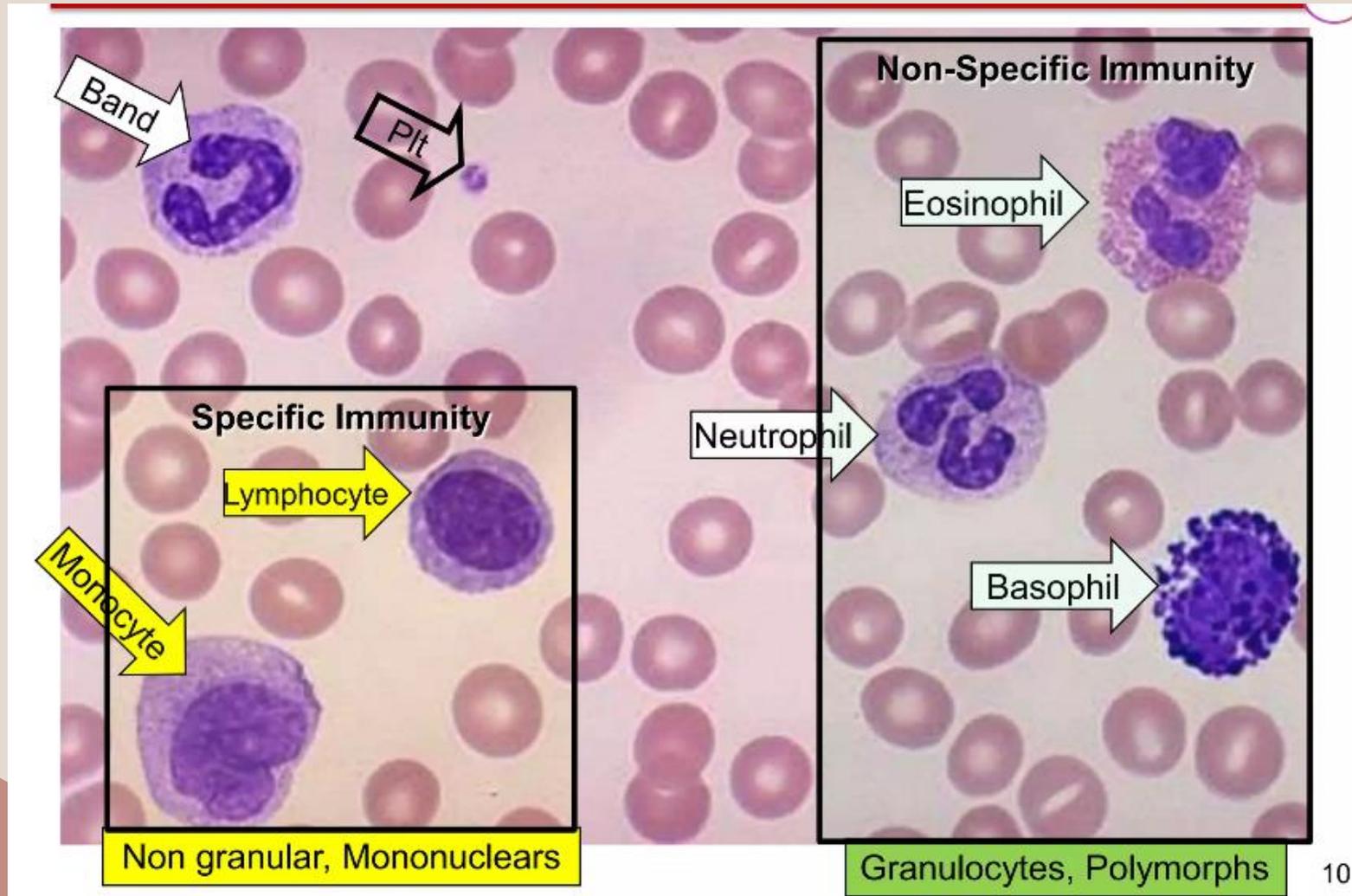
- 1) Proliferation of WBCs and lymph nodes.
 - Reactive: Leukocytosis, Lymphadenitis
 - Neoplastic: Leukemia, Lymphoma.
- 2) Leukopenia: decrease in count of WBCs.
 - Neutropenia, Agranulocytosis

Table 13.1 Adult Reference Ranges for Blood Cells^a

Cell Type	Range
White cells ($\times 10^3/\mu\text{L}$)	4.8–10.8
Granulocytes (%)	40–70
Neutrophils ($\times 10^3/\mu\text{L}$)	1.4–6.5
Lymphocytes ($\times 10^3/\mu\text{L}$)	1.2–3.4
Monocytes ($\times 10^3/\mu\text{L}$)	0.1–0.6
Eosinophils ($\times 10^3/\mu\text{L}$)	0–0.5
Basophils ($\times 10^3/\mu\text{L}$)	0–0.2
Red cells ($\times 10^3/\mu\text{L}$)	
Men	4.3–5
Women	3.5–5
Platelets ($\times 10^3/\mu\text{L}$)	150–450



Normal blood cells



Leukocytosis

- Leukocytosis refers to an increase in the number of white cells in the blood.
 - The bone marrow produces more white blood cells in response to stimulating factors, such as colony-stimulating factors (G-CSF, GM-CSF) and interleukins, released during infection, inflammation, or malignancy.
 - Some growth factors preferentially stimulate the production of a single type of leukocyte. For example, IL-5 mainly stimulates eosinophil production, while G-CSF induces neutrophilia.
-
- as a result, the five principal types of leukocytosis (neutrophilia, eosinophilia, basophilia, monocytosis, and lymphocytosis) tend to be observed in different clinical settings:
 - ✓ Neutrophilia: seen in infection by Pyogenic bacteria
 - ✓ Eosinophilia: seen in Asthma, parasitic infestations, Hodgkin lymphomas
 - ✓ Basophilia: rare
 - ✓ Monocytosis and Lymphocytosis: seen in Tuberculosis.

Lymphadenitis

❖ Lymphoid system consists of:

- 1) Central (primary) lymphoid organs: the bone marrow for B cells and the thymus for T cells
- 2) Peripheral (secondary) lymphoid tissues: lymph nodes, spleen, tonsils, adenoids, and Peyer patches.

❖ The lymphatic system constantly filters fluid (lymph) from the body's tissues. This fluid contains waste products, damaged cells, antigens, and potentially infectious microorganisms.

➤ Upon recognition of an antigen in lymph node, a robust immune response is initiated, leading to several cellular changes:

- Lymphocyte Proliferation: B and T lymphocytes specific to the presented antigen multiply rapidly within the node, causing the follicles and paracortex to expand (reactive lymphoid hyperplasia).
- Leukocyte infiltration: neutrophils and other WBCs are recruited to the L.N to help destroy the pathogen.

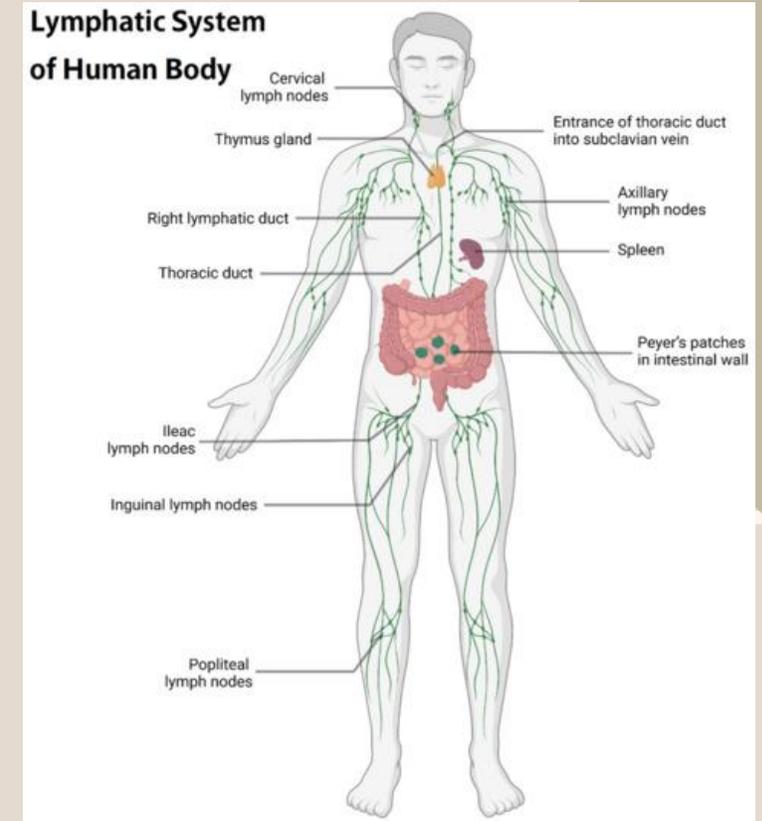
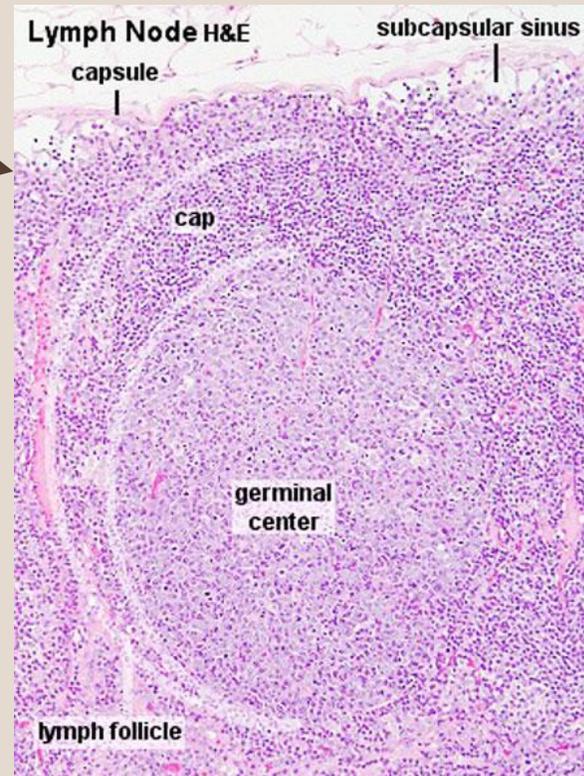
❖ Nodes in specific sites undergo reactive hyperplasia due to:

- **Nodes in cervical region: mostly due to drainage of microbes from infections of the teeth or tonsils,**
- Nodes in the axillary or inguinal regions: mostly caused by infections in the extremities.
- **Mesenteric lymph nodes: acute appendicitis** and other inflammatory conditions involving the gut.

❖ **Two types of lymphadenitis:** Acute (painful), Chronic (painless).

- Clinically: Nodes involved by acute lymphadenitis are swollen and painful.
- When abscess formation is extensive the nodes become fluctuant. The overlying skin is red.
- Sometimes, suppurative infections penetrate through the capsule of the node and track to the skin to produce draining sinuses. Healing of such lesions is associated with scarring

- Histologically: large follicles with pale germinal center, and mantle zone



Neutropenia, Agranulocytosis

- Neutropenia, a reduction in the number of neutrophils in the blood
- Agranulocytosis, a marked reduction in neutrophils, has the serious consequence of making individuals susceptible to bacterial and fungal infections
- Neutropenia can be caused by:
 - (1) decreased production: marrow aplasia or drugs.
 - (2) increased destruction: autoimmunity
- The most common cause of agranulocytosis is drug toxicity (alkylating agents and antimetabolites used in cancer treatment)
- Clinically: susceptible to infections, oral ulcer with white thick pus (pseudomembrane) of bacteria or fungus (candida)



Neoplastic proliferation

❖ Hemato-oncology (blood cancer)

1) Leukemia: normal bone marrow replaced by immature and undifferentiated leukocytes or **blast cells**. These blasts then circulates in the blood and infiltrate the blood forming organs (liver, spleen, lymph nodes) and other sites throughout the body.

- Two major types: Myeloid and Lymphoid
- Two presentation: Acute and Chronic (AML, CML, ALL, CLL)

2) Lymphoma:

- Solid tumor of lymphoid tissue
- example: Hodgkin and Non-Hodgkin lymphoma.

3) Premalignant disorders:

- MPD Myelo-proliferative Disease: Excess proliferation, more abnormal cells.
- MDS Myelo-Dysplastic Syndrome: Dysplastic (abnormal cells), Pancytopenia.

1# Leukemia

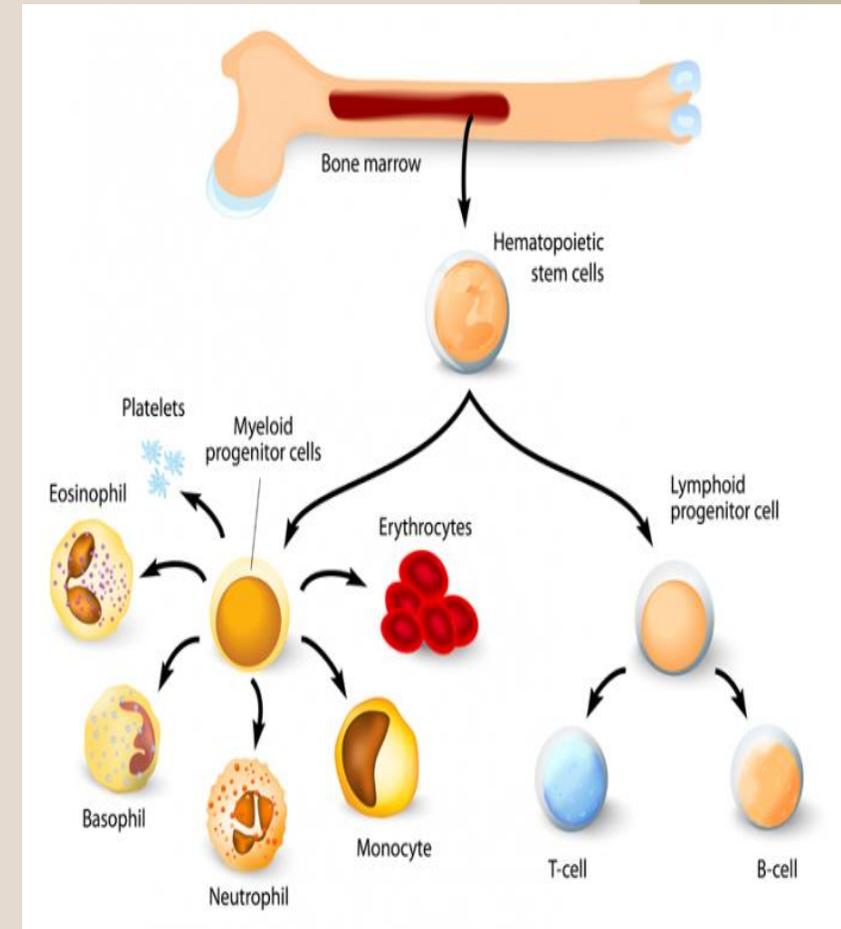
- Leukemia is a cancer caused by replacement of bone marrow by immature and undifferentiated leukocytes or **blast cells**

- Two major types:

- 1) Lymphocytic (affecting cells that become lymphocytes)
- 2) Myelogenous (affecting cells that mature into other types of blood)

- Two presentation: Acute (progressing quickly) and Chronic (developing slowly)

- **In adults**, chronic lymphocytic leukemia (CLL) and acute myelogenous leukemia (AML) are the most common leukemia.
- **In children**, the most common leukemia is acute lymphoblastic leukemia (ALL).

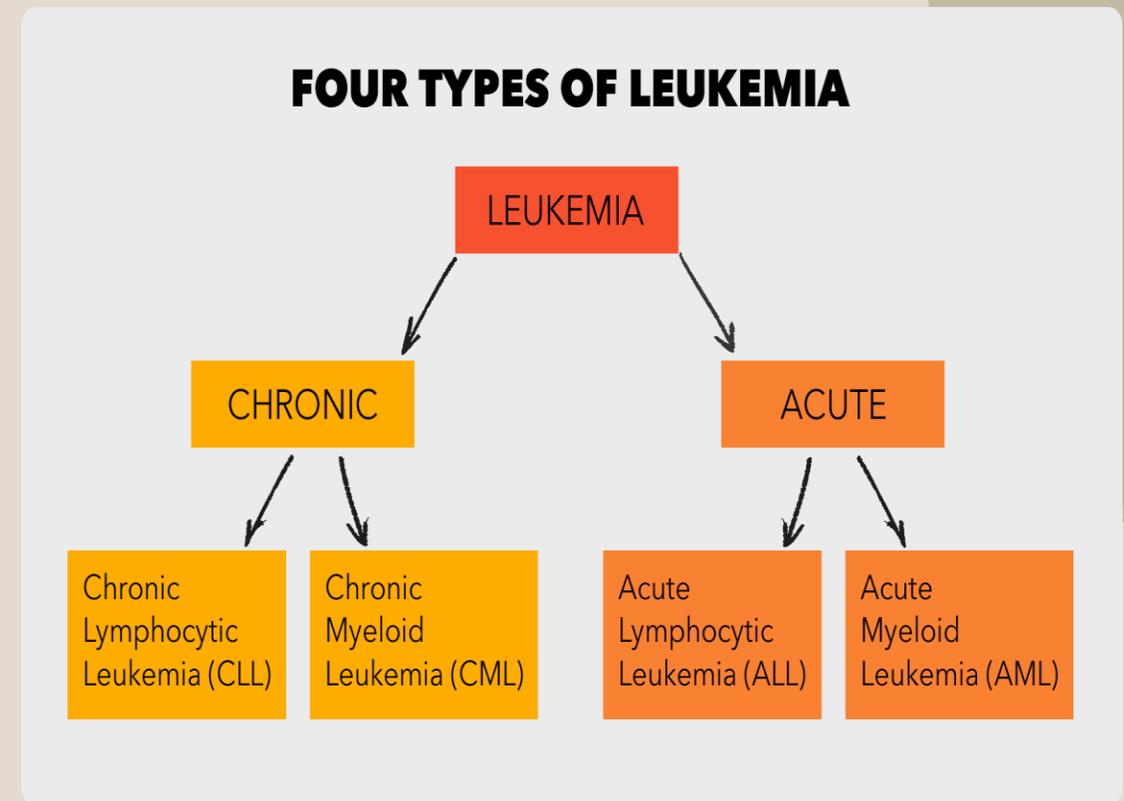


- Sign and symptoms of Leukemia relate to:
- Problems caused by bone marrow failure: Overcrowding by abnormal cells, inadequate production of normal marrow elements **so** anemia, thrombocytopenia, ↓ number and function of WBCs.
- Relate to problems caused by leukemic cells infiltrate patient's organs: Splenomegaly, hepatomegaly, lymphadenopathy, bone pain, meningeal irritation.
- Suspect Leukemia on CBC in case of: Pancytopenia, or abnormal WBCs count, extreme high or low

Risk factors:

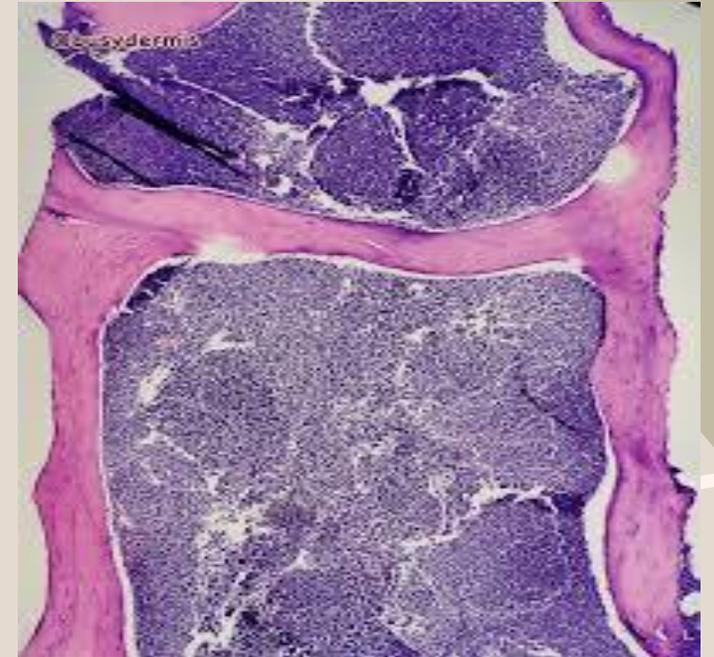
Combination of predisposing factors including genetic and environmental influences:

1. Chronic exposure to chemical such as benzene
2. Radiation exposure.
3. Cytotoxic therapy of breast, lung and testicular cancer.
4. Congenital anomaly
5. The presence of primary immunodeficiency and infection with the human T –cell leukemia virus type-1



Acute lymphoblastic leukemia (ALLs)

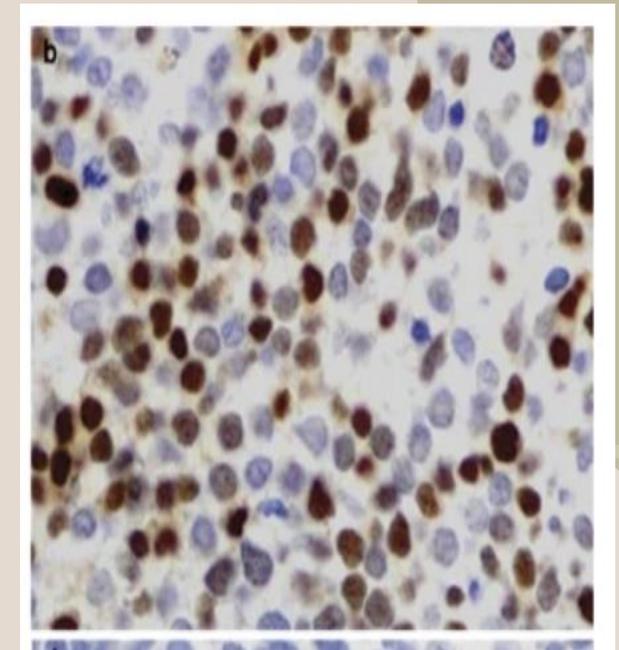
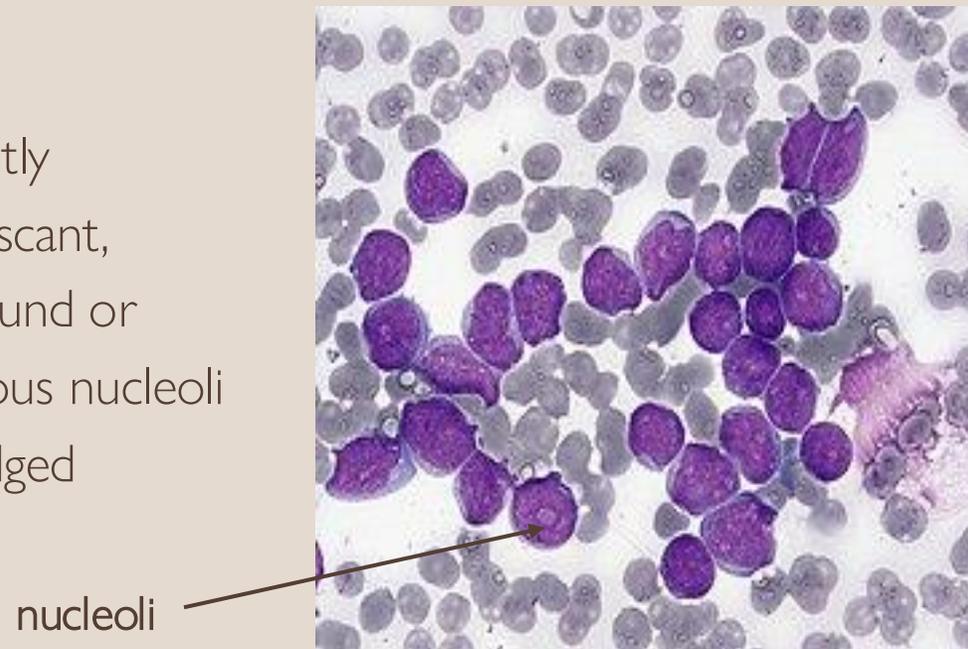
- They are neoplasms composed of immature B (pre-B) or T (pre-T) cells, which are referred to as **lymphoblasts**
- Progenitor B cell Derived ALL constitutes 80-85% ALL (the most common), 15% are derived from T Cells.
- the most common childhood malignancy
- Increased risk of leukemia (ALL and AML) in children with down syndrome.
- Prognostic factors:
- Bad prognosis:
 - 1) infancy (less than 1 yr old) and adult age,
 - 2) central nervous system involvement at the time of diagnosis,
 - 3) leukocyte count more than 50,000/mm³ at diagnosis
- Favorable prognosis: Children between the ages of 1 and 9 yrs.



Bone marrow — 12
replacement by blasts

- Diagnosis:
- Clinical presentation: Children may present with pancytopenia or hyperleukocytosis
- The diagnosis is confirmed by peripheral smear examination, bone marrow aspirate and biopsy.
- Bone marrow biopsy findings:
- the marrow is hypercellular and packed with lymphoblasts, which replace normal marrow elements
- Bone marrow showing >25% lymphoblasts is diagnostic for ALL.

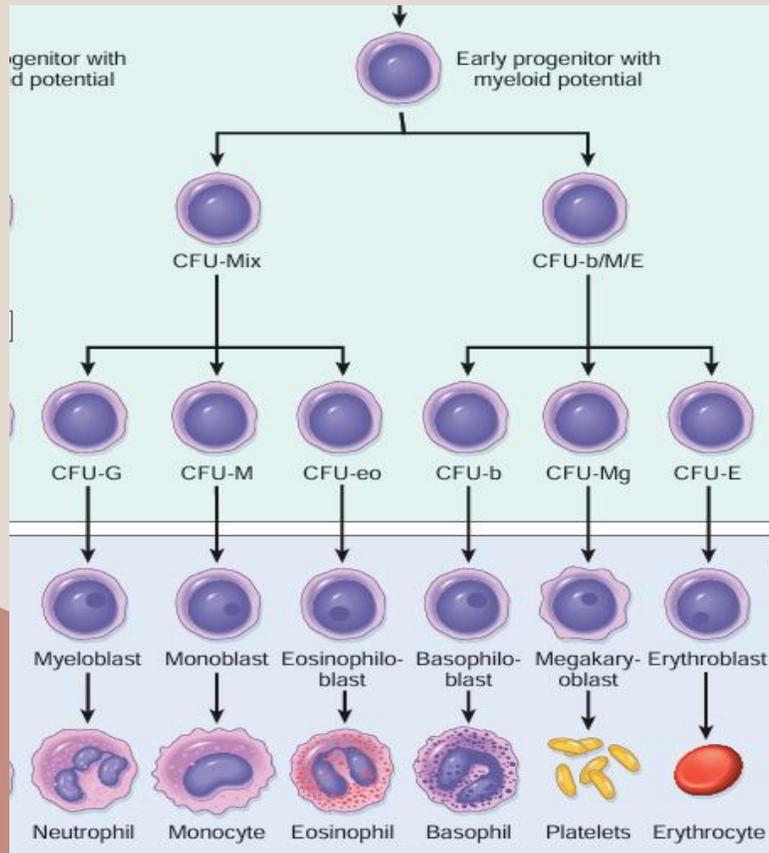
- Neoplastic lymphoblasts are slightly larger than lymphocytes and have scant, faintly basophilic cytoplasm and round or convoluted nuclei with inconspicuous nucleoli and fine chromatin, often in a smudged appearance



TdT positive blasts

Acute Myeloid Leukemia (AML)

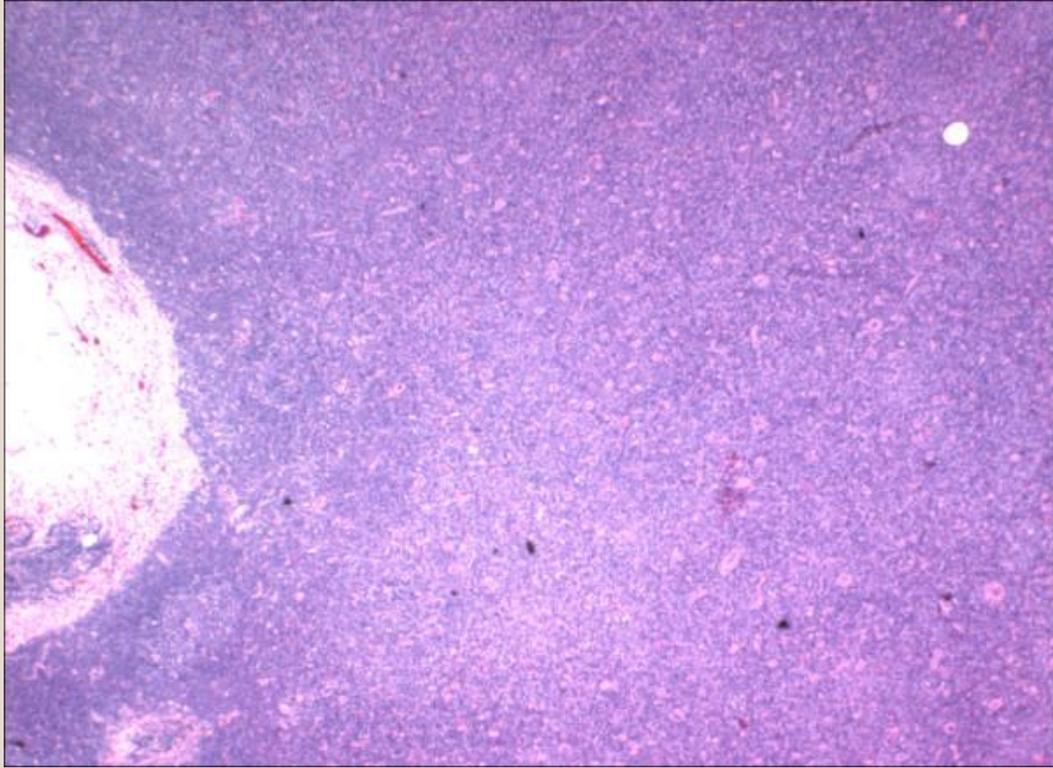
- Characterized by the development of immature **myeloblasts** in the bone marrow.
- Diagnosis:
Low RBC, Hb, low platelet count, low to high WBC count with myeloblasts.



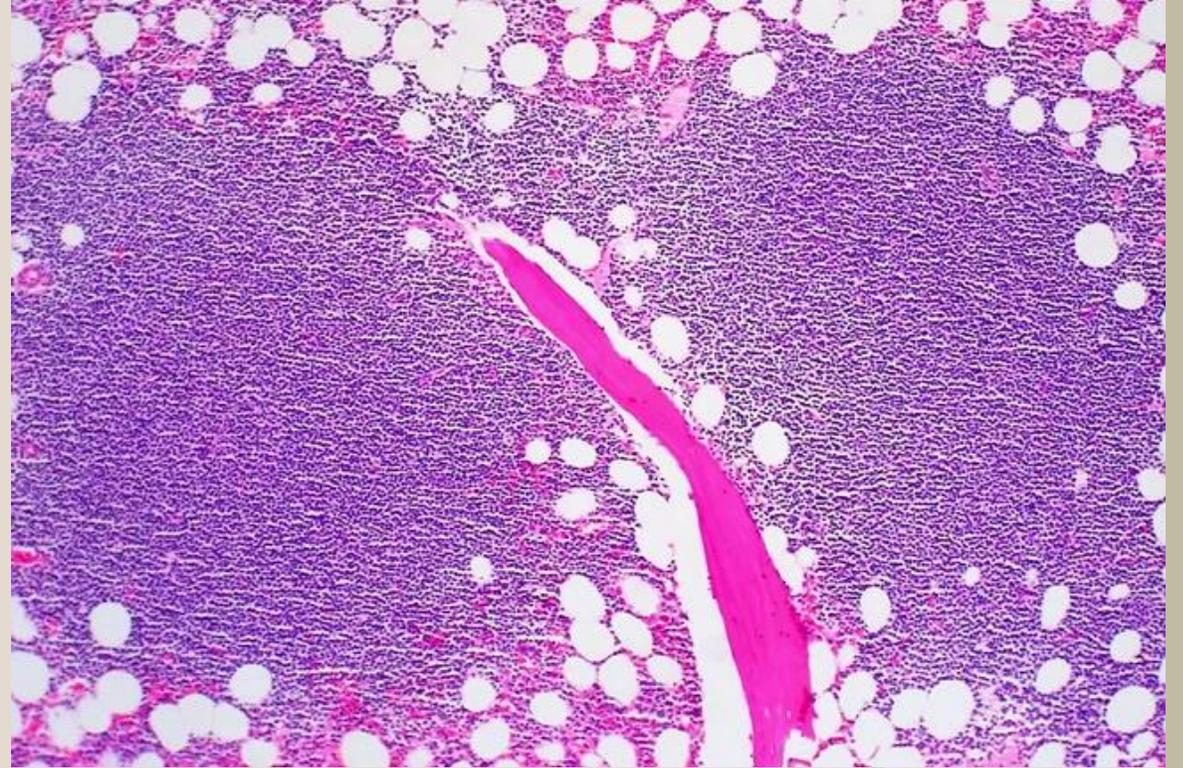
M0	Undifferentiated AML
M1	AML with minimal maturation
M2	AML with maturation
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryocytic leukemia

Chronic lymphocytic Leukemia (CLL)/SLL

- The incidence of CLL increases with age more than 60 and is rare under the age of 35. It is common in men.
- Pathophysiology
- It is characterized by proliferation of small, abnormal, **mature B lymphocytes**, often leading to decreased synthesis of immunoglobulin and depressed antibody response.
- CLL: The number of mature lymphocytes in peripheral blood smear and bone marrow are greatly increased (more than $5 \times 10^3 / \mu\text{l}$) with or without nodal involvement.
- Small lymphocytic lymphoma (SLL): $< 5 \times 10^3$ CLL-like cells in peripheral blood with nodal or extranodal manifestation, usually with bone marrow involvement.
- Laboratory findings:
- Anemia
- Thrombocytopenia.
- The WBC count is elevated to a level between 20,000 to 100,000 with lymphocytosis



Lymph node effaced by mature B cell infiltration.



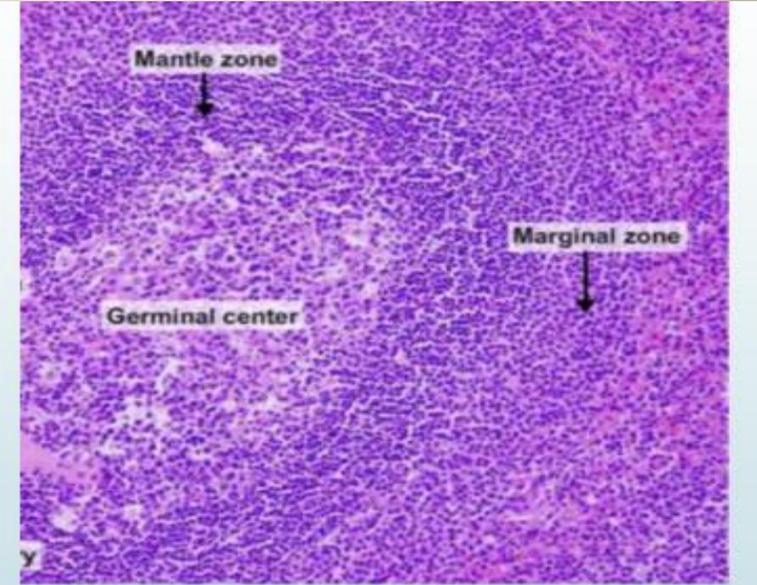
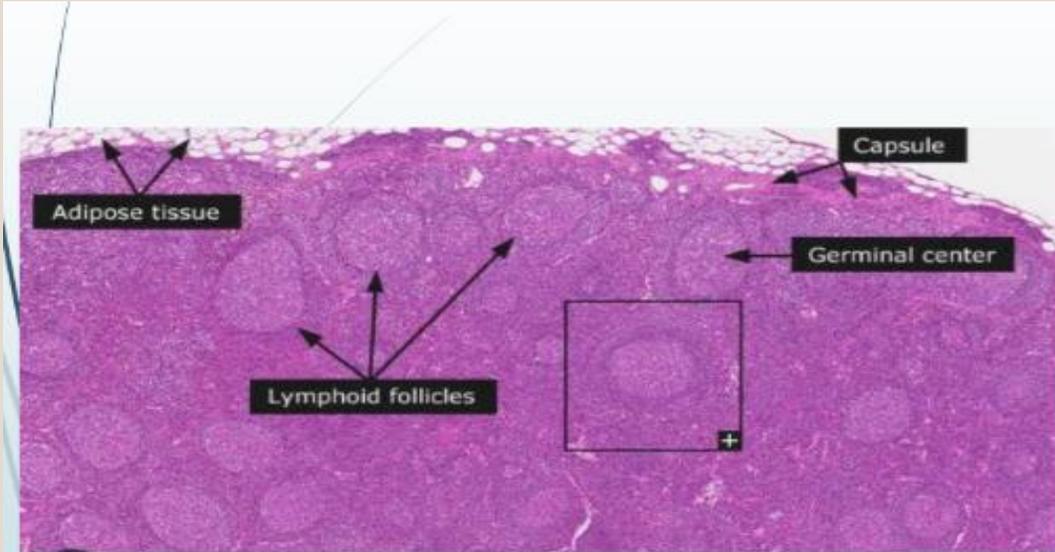
Bone marrow involvement by CLL

Chronic Myelogenous Leukemia (CML)

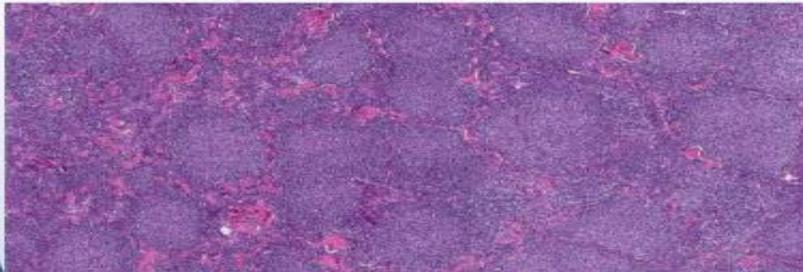
- CML is distinguished from other myeloproliferative neoplasms by the presence of a chimeric **BCR-ABL gene** derived from portions of the BCR gene on chromosome 22 and the ABL gene on chromosome 9 (**Philadelphia chromosome**)
- Clinical findings:
- Leukocytosis with predominant neutrophils and myelocytes
- Basophilia and eosinophilia
- Platelet counts are normal or increased to $> 1000 \times 10^9/\mu\text{l}$
- The bone marrow is hypercellular owing to increased numbers of maturing granulocytic and megakaryocytic precursors.
- **Massive splenomegaly:** The red pulp of the enlarged spleen resembles bone marrow because of the presence of extensive **extramedullary hematopoiesis**.

2# Lymphoma

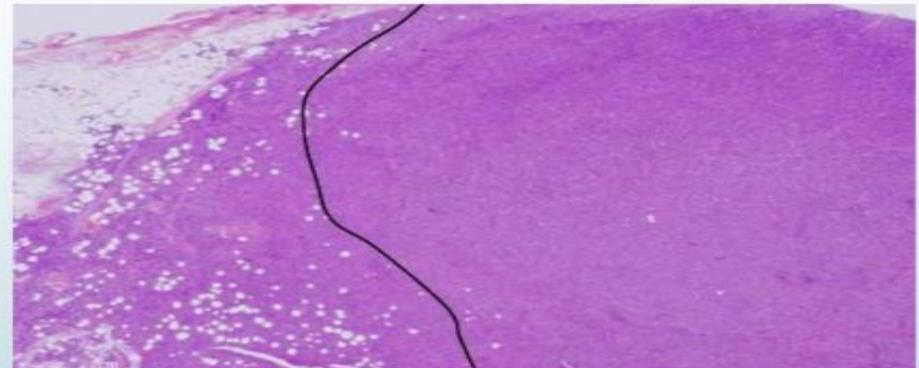
Normal Lymph Node



Lymphoma :disturbed architecture



nodular



Diffuse

Lymphoma



Hodgkin lymphoma

Classical

Nodular sclerosing

Lymphocyte rich

Mixed cellularity

Lymphocyte depleted

Nodular lymphocyte predominant

Non-Hodgkin lymphoma

B Cell

Low grade

Chronic lymphocytic leukaemia/small lymphocytic lymphoma

★ Follicular

Extranodal marginal zone

Mantle cell

High grade

★ Diffuse large B cell

Burkitt

T Cell

★ Mycosis fungoides

Anaplastic large cell

Follicular lymphoma

- Follicular lymphoma is the most common form of indolent NHL
- Follicular lymphoma is strongly associated with chromosomal translocations involving BCL2.
- BCL2 antagonizes apoptosis and promotes the survival of follicular lymphoma cells. Notably, while normal germinal centers contain numerous B cells undergoing apoptosis, follicular lymphoma is characteristically devoid of apoptotic cells.

- Clinically:
 - Older than 50 yrs
 - Generalized painless lymphadenopathy
 - Bone marrow involvement occurs in 85% of cases. The spleen and liver are also frequently involved
- Incurable lymphoma

- **Note: indolent lymphoma meaning:** type of slow-growing non-Hodgkin lymphoma with few symptoms, often requiring no immediate treatment.

- Morphology:

- Lymph nodes usually are effaced by a distinctly nodular (follicular) proliferation

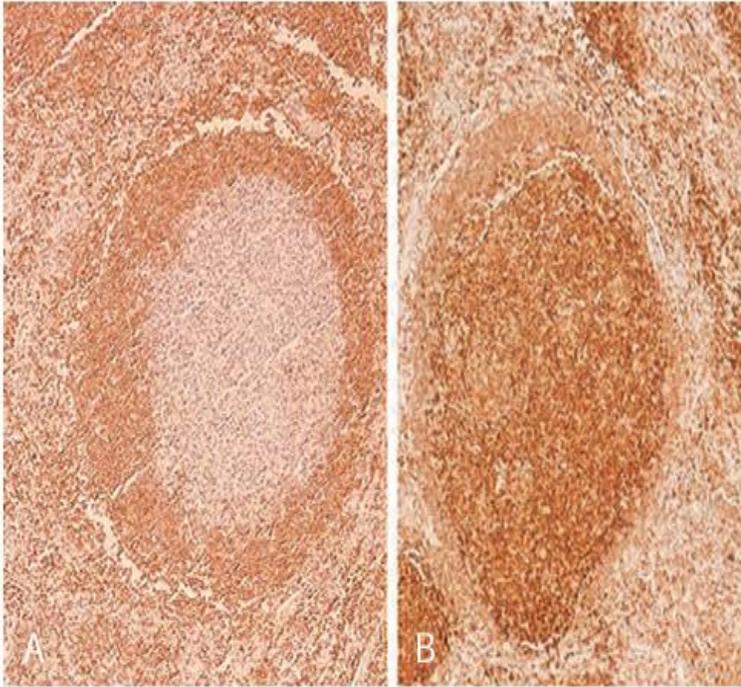
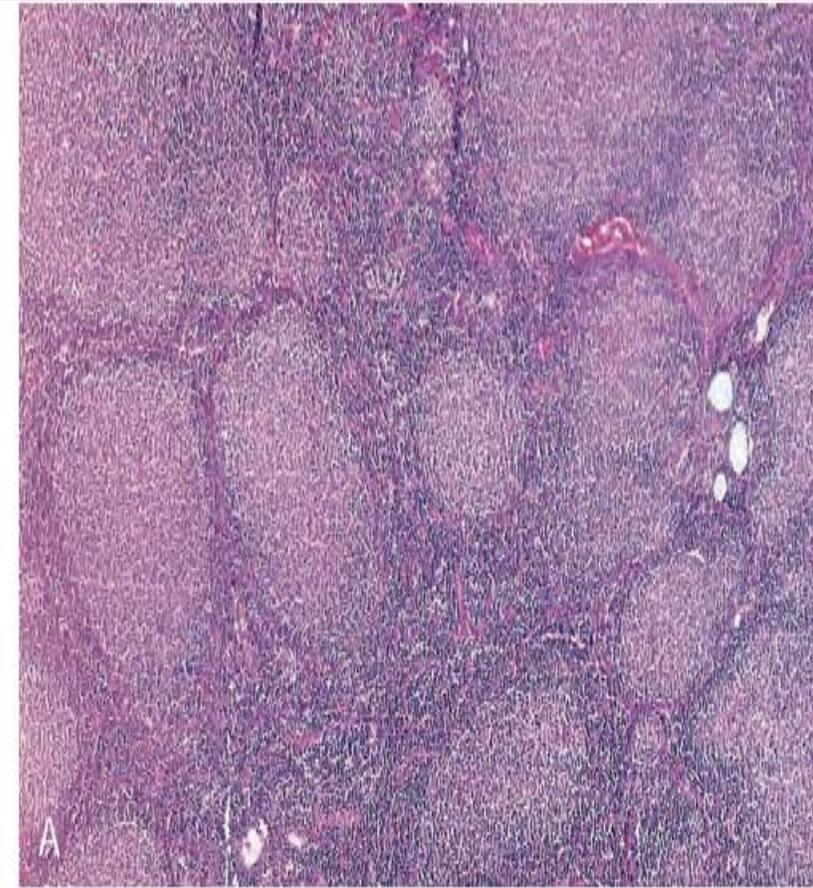


Figure 13.12 BCL2 expression in reactive and neoplastic follicles. BCL2 protein was detected by using an immunohistochemical technique that produces a brown stain. In reactive follicles (A), BCL2 is present in mantle zone cells but not follicular-center B cells, whereas follicular lymphoma cells (B) show strong BCL2 staining. (Courtesy Dr. Jeffrey Jorgenson,

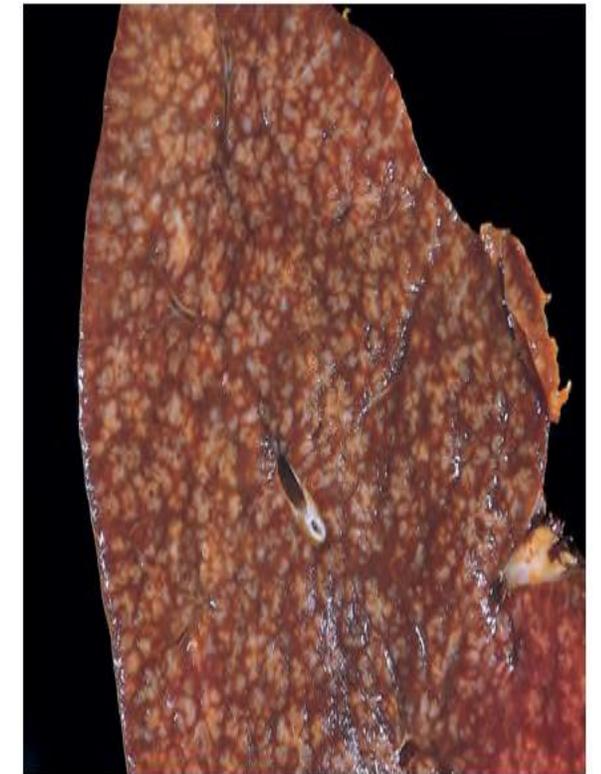


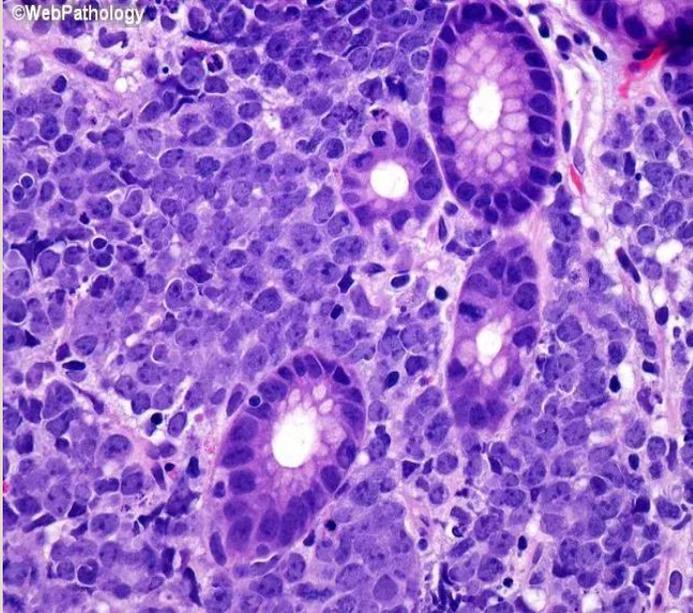
Figure 13.11 Follicular lymphoma (spleen). Prominent nodules represent white pulp follicles expanded by follicular lymphoma cells. Other indolent

Diffuse Large B cell Lymphoma (DLBCL)

- Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL
- Arise either de novo or transformation from other low grade tumors (follicular lymphoma).
- Pathogenesis: Mutations & rearrangements of the **BCL6 gene**
- An aggressive and rapidly fatal lymphoma if not treated
- With intensive chemotherapy 60% to 80% of patients achieve complete remission, and up to 50% can be cured.
- Typically presents as a rapidly enlarging mass at a nodal or extranodal site



- Morphology:
- Diffuse infiltration by large neoplastic B cells (three to four times the size of resting lymphocytes).



DLBCL in GI

DLBCL in Node
showing diffuse
infiltration and effaced
architecture

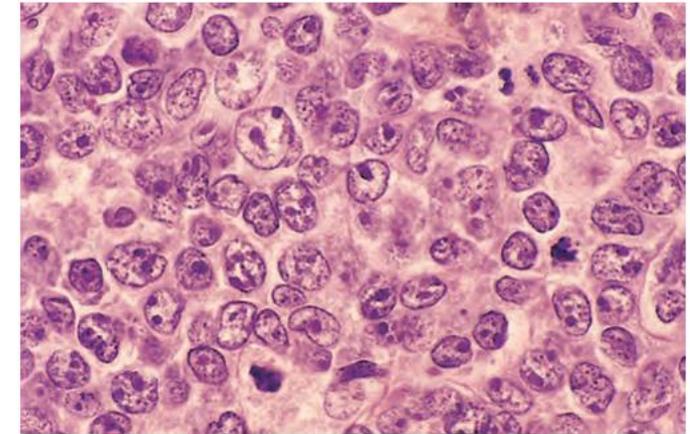
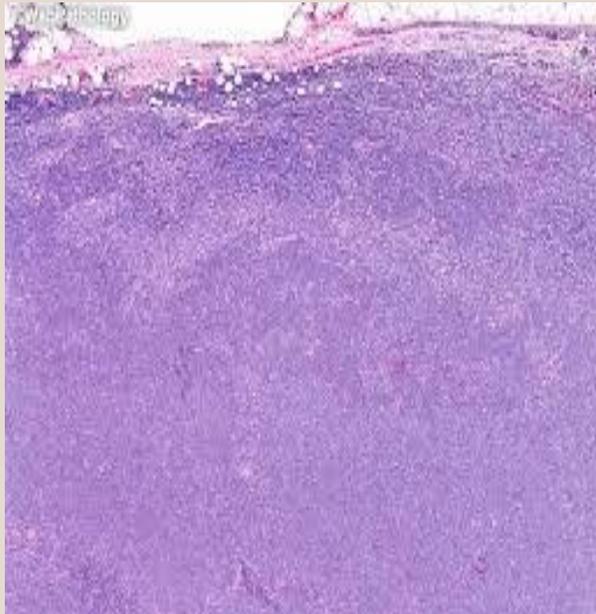
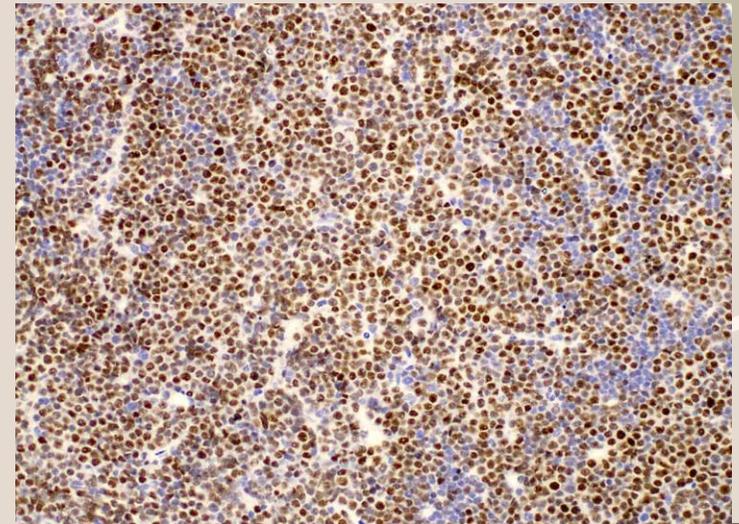


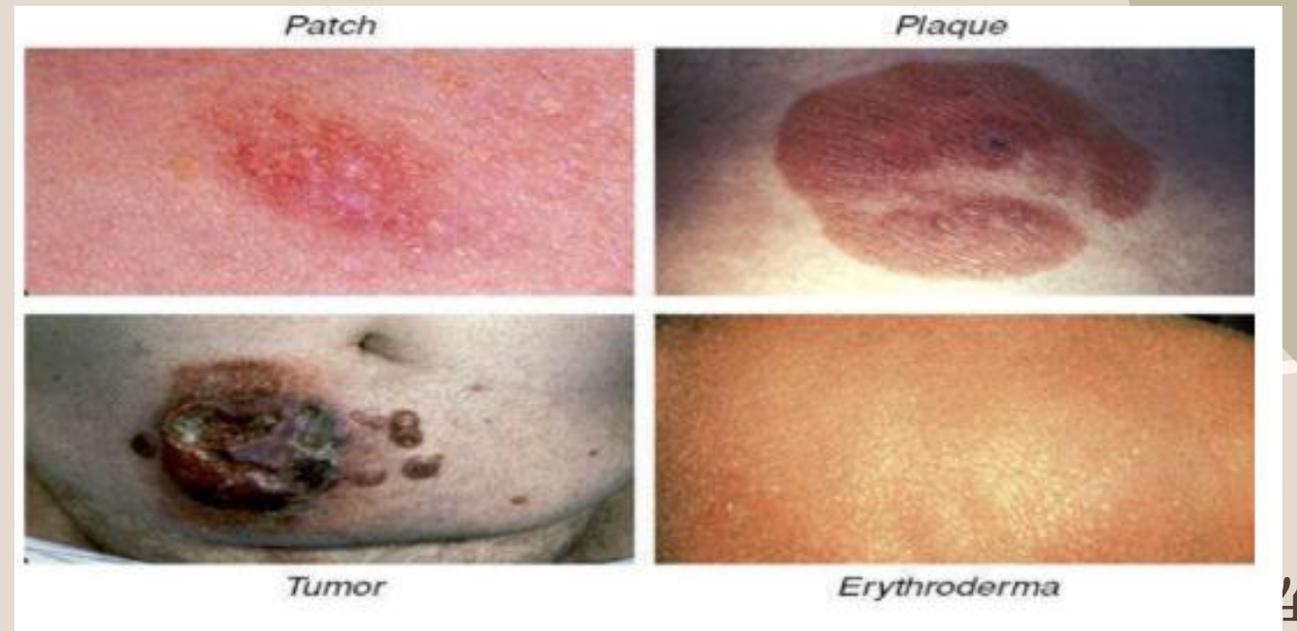
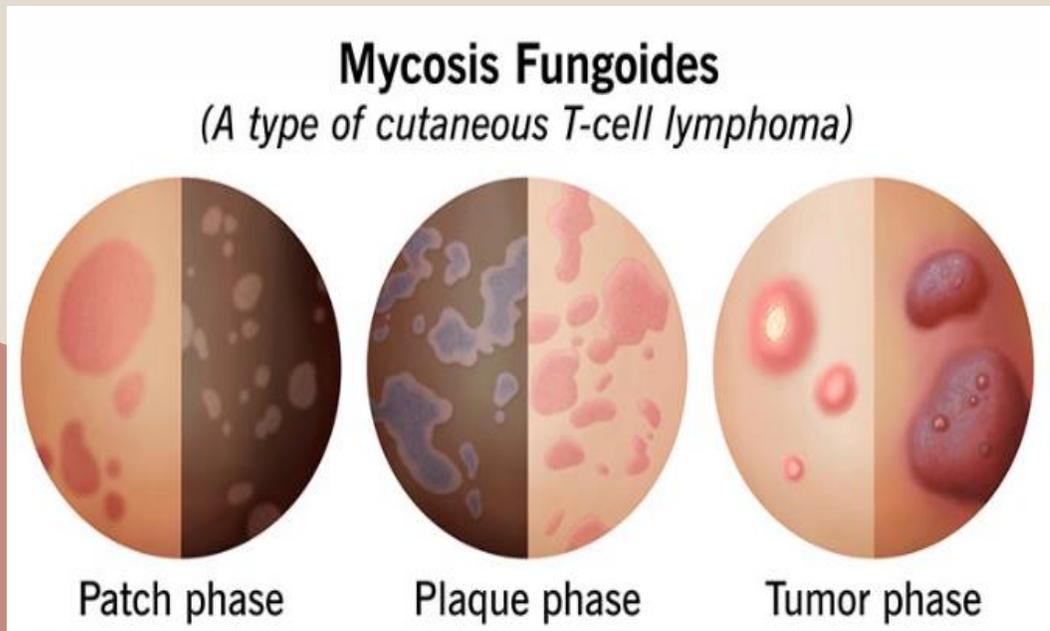
Figure 13.13 Diffuse large B-cell lymphoma. Tumor cells have large nuclei, open chromatin, and prominent nucleoli. (Courtesy Dr. Robert W.



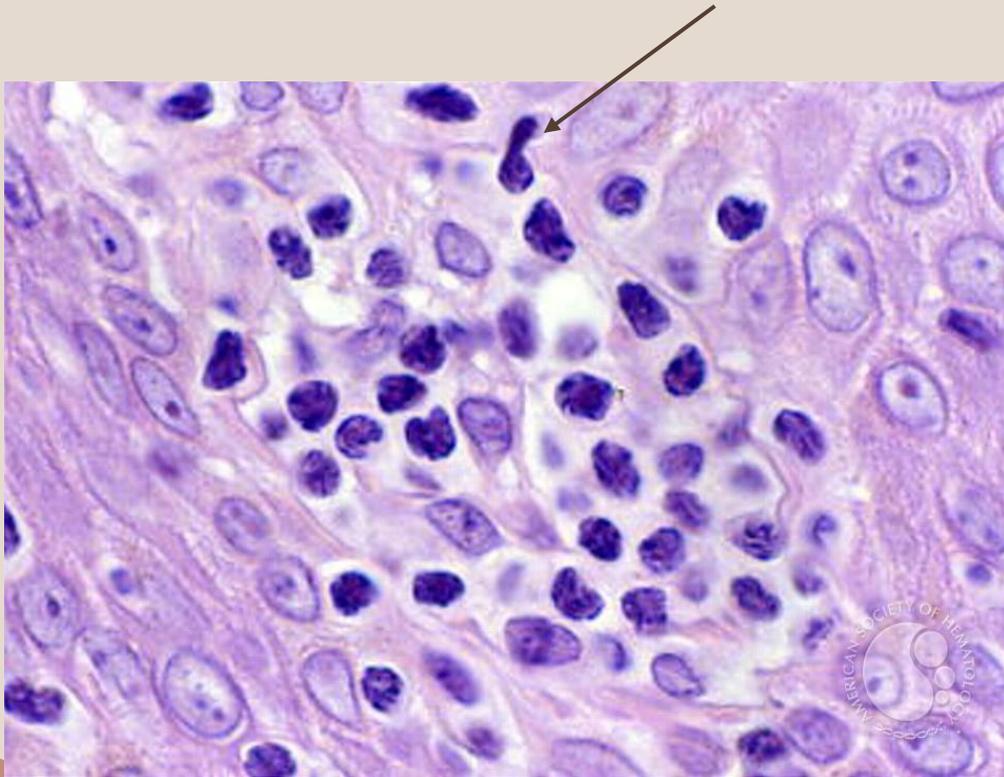
BCL6

T cell cutaneous lymphoma

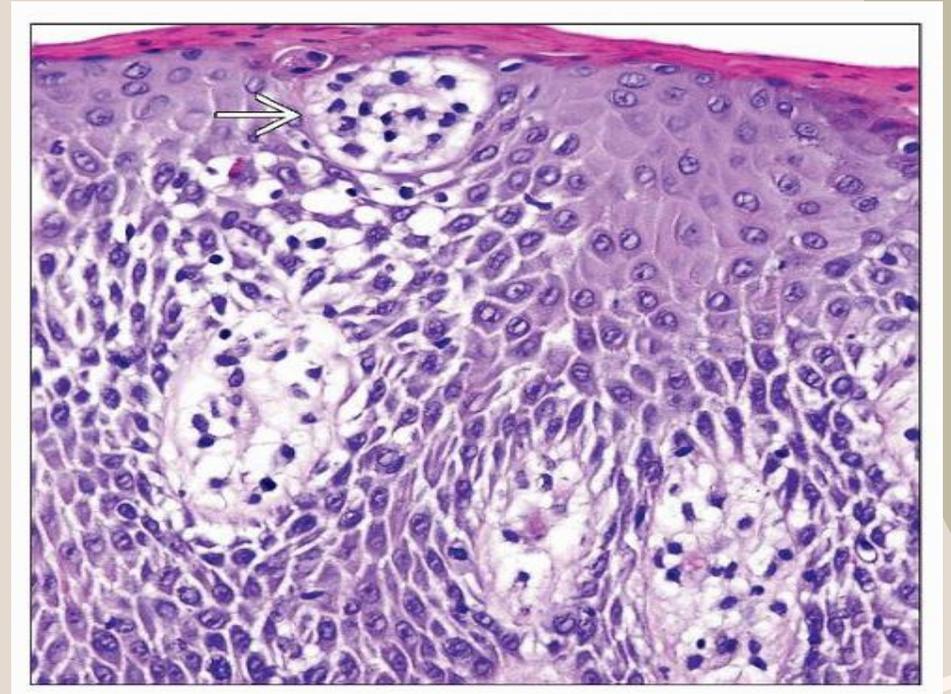
- Mycosis Fungoides :
- Peripheral T cell lymphoma derived from mature, post-thymic T lymphocytes
- Presents as cutaneous patches and can progress to plaques and tumors and erythroderma



- Morphology:
- Infiltration of epidermis & upper dermis by neoplastic T cells with marked infoldings of the nuclear membranes → a **cerebriform appearance**.



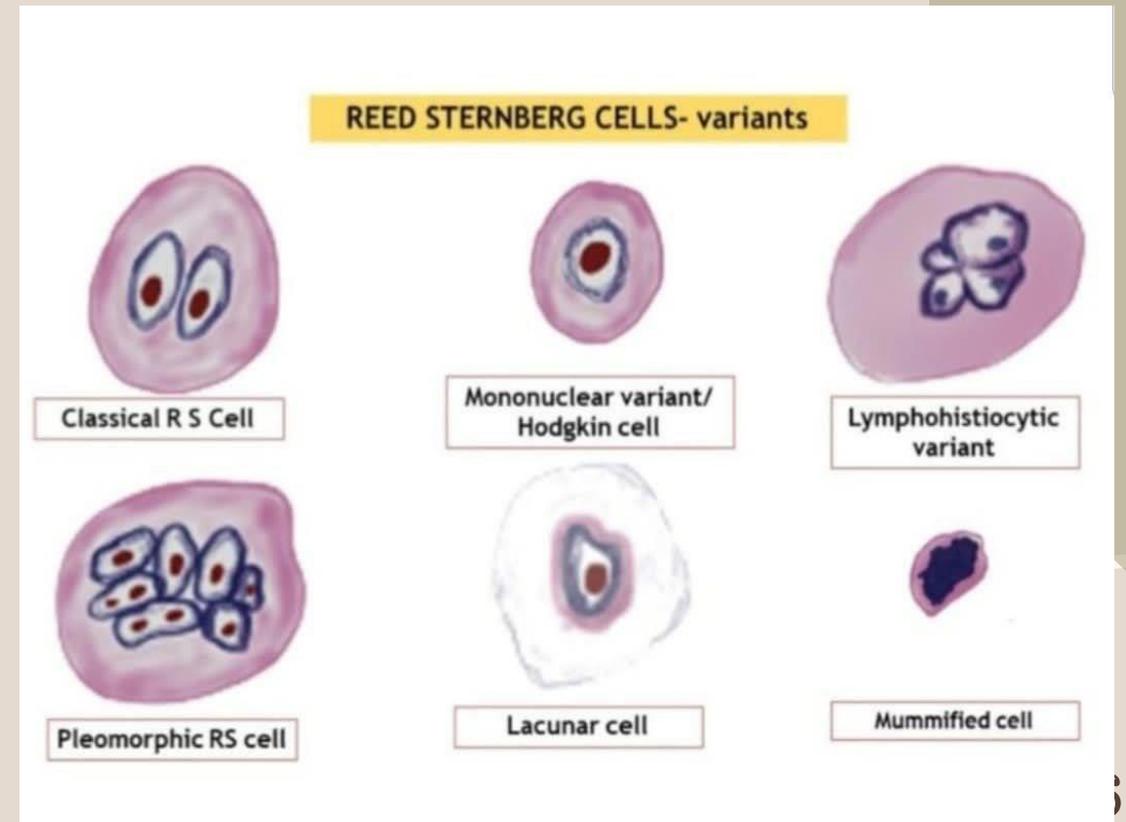
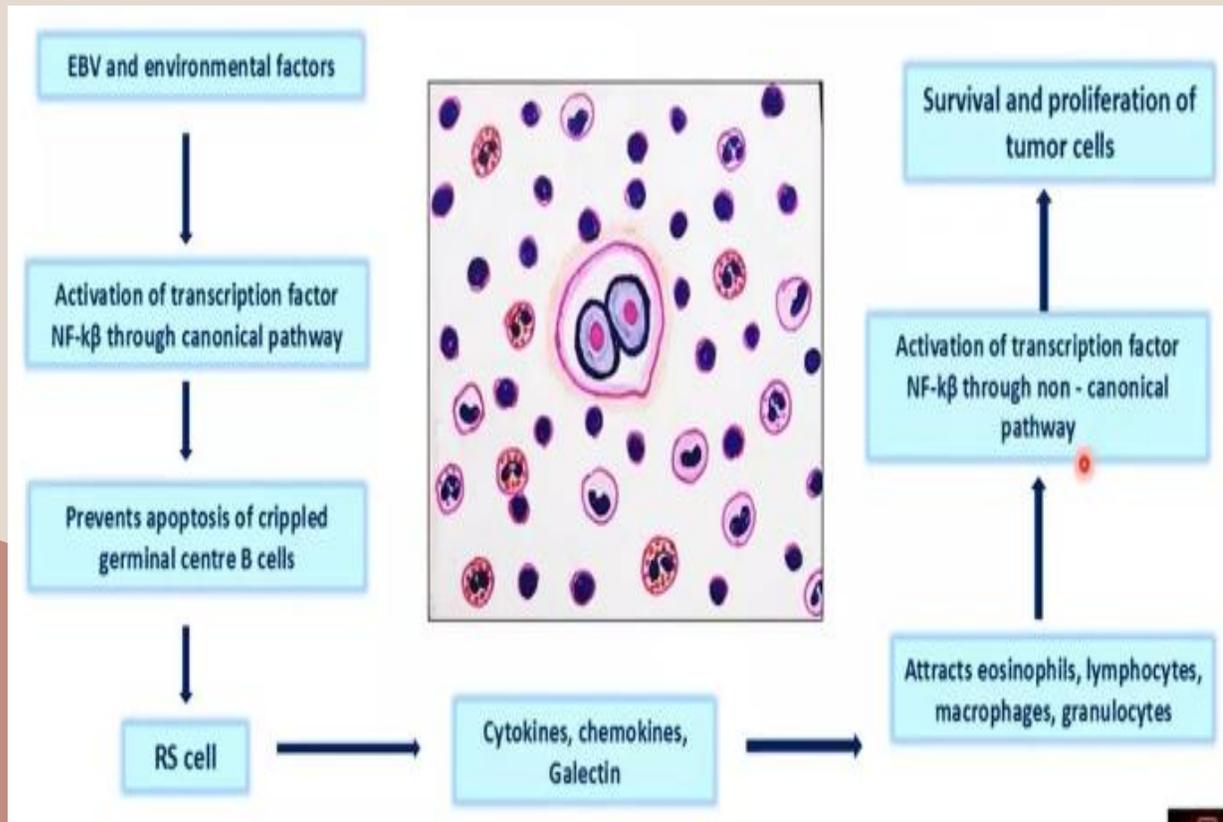
Cerebriform cells



Infiltration of epidermis

Hodgkin's lymphoma

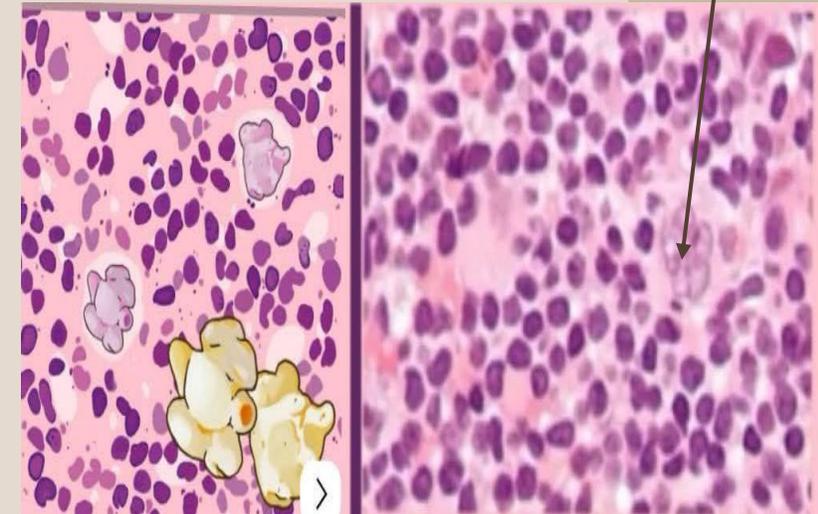
- Disease mainly arises in lymph nodes from B-cells and secondary involves extra nodal sites
- Characterized by heterogeneous cellularity: Majority of cells are non-neoplastic + Minority of cells are neoplastic, called Reed-Sternberg or Hodgkin cells



- WHO classification divides Hodgkin lymphoma into two main types:
 - 1) Non classical: Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)
 - 2) Classical Hodgkin Lymphoma (CHL) includes:
 - Nodular Sclerosis
 - Mixed Cellularity
 - Lymphocyte Rich
 - Lymphocyte Depleted

Non-classical: Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

- Represents 10% of all Hodgkin lymphoma cases
- Male to female ratio is 3:1
- Typically presents as localized disease in peripheral lymph nodes (cervical, axillary, inguinal)
- Morphology: characterized by Popcorn cells: The neoplastic cells have large, irregular nuclei that, under a microscope, appear to have a lobed or "popped" shape, absent sclerosis and necrosis.



- Classical Hodgkin Lymphoma (CHL)

- Represents 90% of Hodgkin lymphoma cases
- B symptoms present in about 40% of patients
- Aggressive disease but generally curable
- Reed Sternberg Cells & Variants: + Background Cells (Predominantly T lymphocytes, variable histiocytes, plasma cells, eosinophils, neutrophils)
- Tissue Features: Presence of sclerosis and possible necrosis

B symptoms:

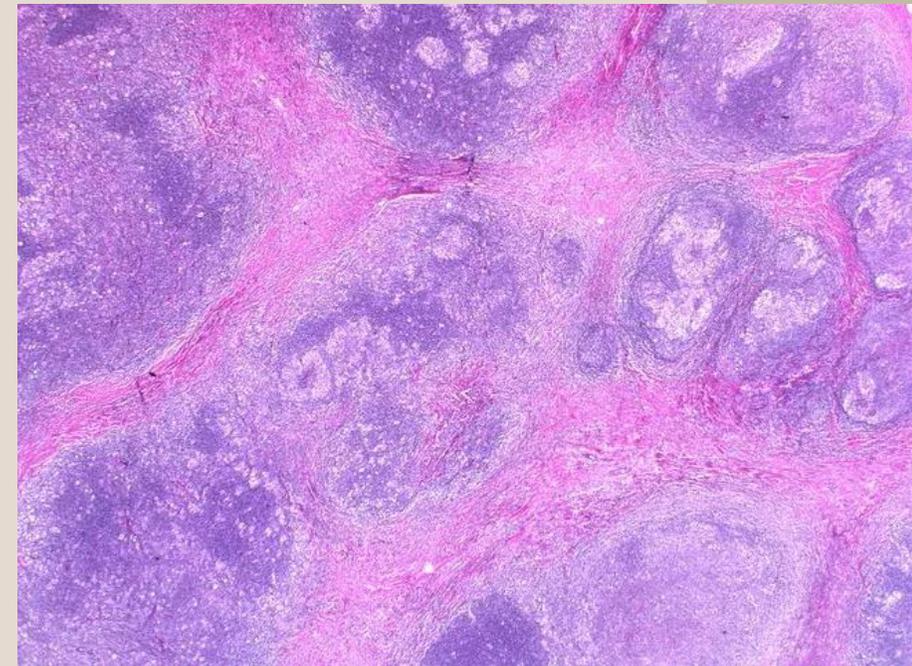
Unexplained fever

Drenching night sweats

Unintentional weight loss >10% in 6 months

1) Nodular sclerosis:

- Affects adolescents and young adults; more common in females
- Mediastinum frequently involved
- Epstein-Barr Virus (EBV) present in 10-25% of cases
- Morphology: Nodular growth pattern with broad collagen bands/
Presence of lacunar cells.

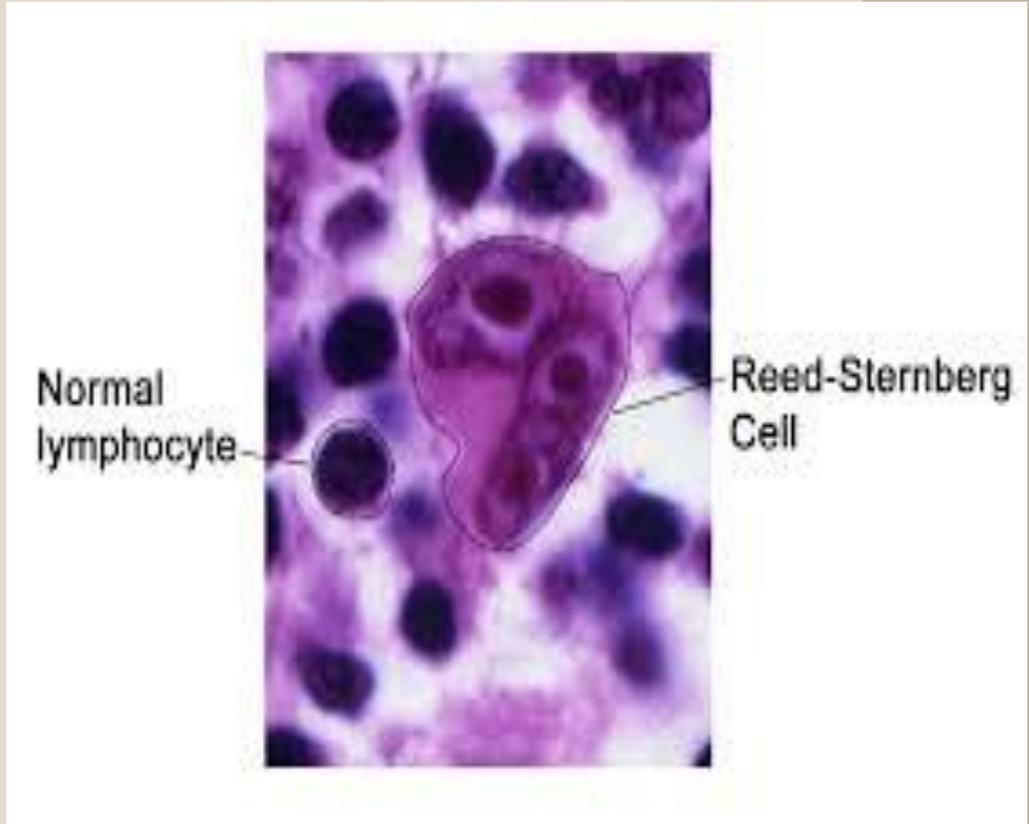


- 2) Mixed cellularity:
 - Most frequent in older adults
 - Strongest association with Epstein-Barr Virus (EBV), with 75% of cases EBV-positive
 - Morphology: Diffuse or interfollicular proliferation of Hodgkin and Reed-Sternberg (HRS) cells, comprising less than 10% of total cellularity.
- 3) Lymphocyte Rich:
 - Usually presents as localized disease without bulky masses or B symptoms
 - Prognosis slightly better than other classical Hodgkin lymphoma types, resembling NLPHL
- 4) Lymphocyte depleted:
 - Occurs mainly in HIV+ patients.
 - Characterized by widespread disease with peripheral and/or internal lymphadenopathy
 - Morphology: Predominance of Hodgkin-Reed Sternberg (HRS) cells with few background lymphocytes.

Table 13.9 Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification)

Stage	Distribution of Disease
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm without (III) or with (IIIE) localized involvement of an extralymphatic organ or site
IV	Diffuse involvement of one or more extralymphatic organs or sites with or without lymphatic involvement

All stages are further divided on the basis of the absence (A) or presence (B) of the following symptoms: unexplained fever, drenching night sweats, and/or unexplained weight loss of greater than 10% of normal body weight.



- With current treatment protocol, tumor stage rather than histologic type is the most important prognostic variable
- Cure rate for stages I and IIA is nearly 90%
- Disease-free survival at 5 years for stages IVA and IVB is 60% to 70%

3# Myeloproliferative diseases:

- A group of disorders characterized by the presence of mutated, constitutively activated tyrosine kinases lead to growth factor independence.
- Four major diagnostic entities are recognized:
 - 1) Chronic myeloid leukemia (CML).
 - 2) Polycythemia vera (PCV).
 - 3) Primary myelofibrosis (PM).
 - 4) Essential thrombocythemia (ET).
- all MPNs have variable propensities to transform to:
 - 1) a “spent phase”: resembling primary myelofibrosis
 - 2) a “blast crisis” identical to AML
- ▶ Both triggered by the acquisition of other somatic mutations

Polycythemia vera:

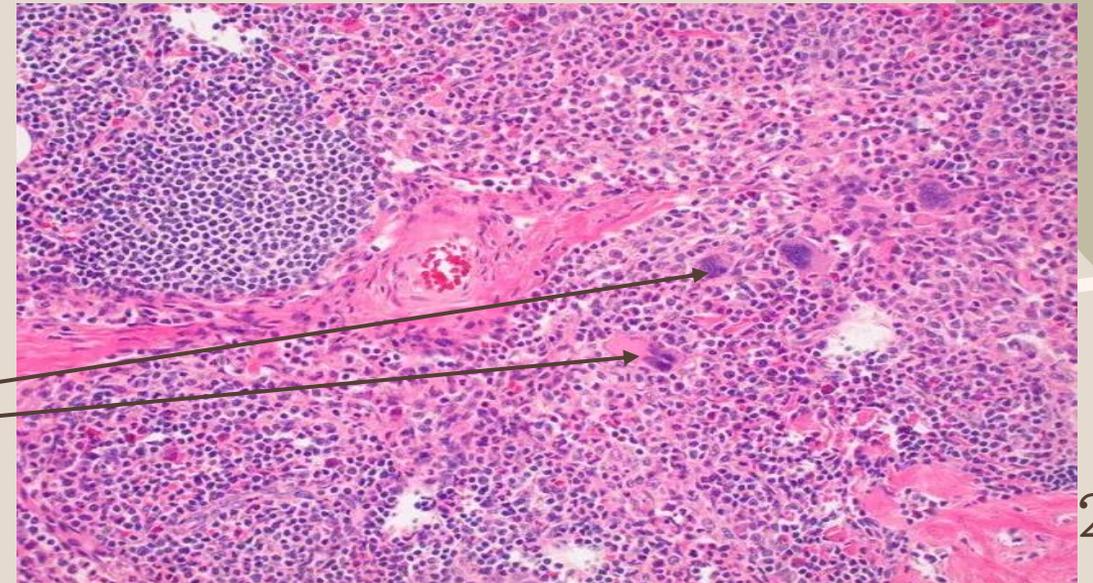
- Excessive proliferation of erythroid, granulocytic, and megakaryocytic elements in bone marrow.
- Unlike secondary forms of polycythemia, in which erythropoietin levels are high, PCV is associated with low serum erythropoietin
- Mutations in the tyrosine kinase JAK2 (lowers the dependence of hematopoietic cells on growth factors for growth and survival) in 95% of patients.
- **Clinically:** most clinical signs & symptoms are related to an absolute increase in red cell mass.
- Hepatomegaly & small foci of extramedullary hematopoiesis / Thromboses & infarctions are common / plethoric face / Purities)due to increased histamine from basophils)



plethora

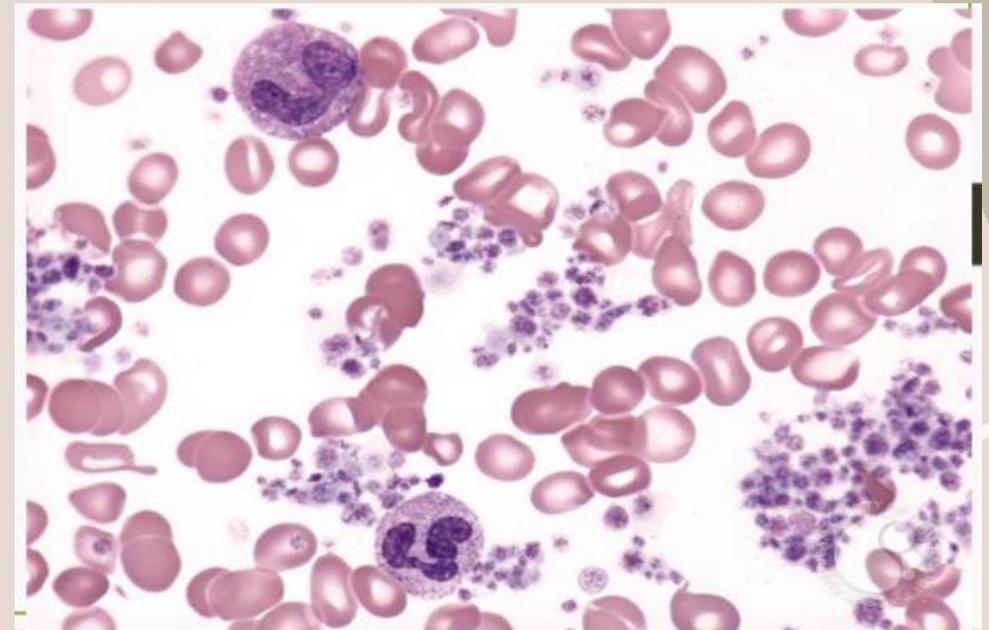
Extramedullary
hematopoiesis

Megakaryocytes



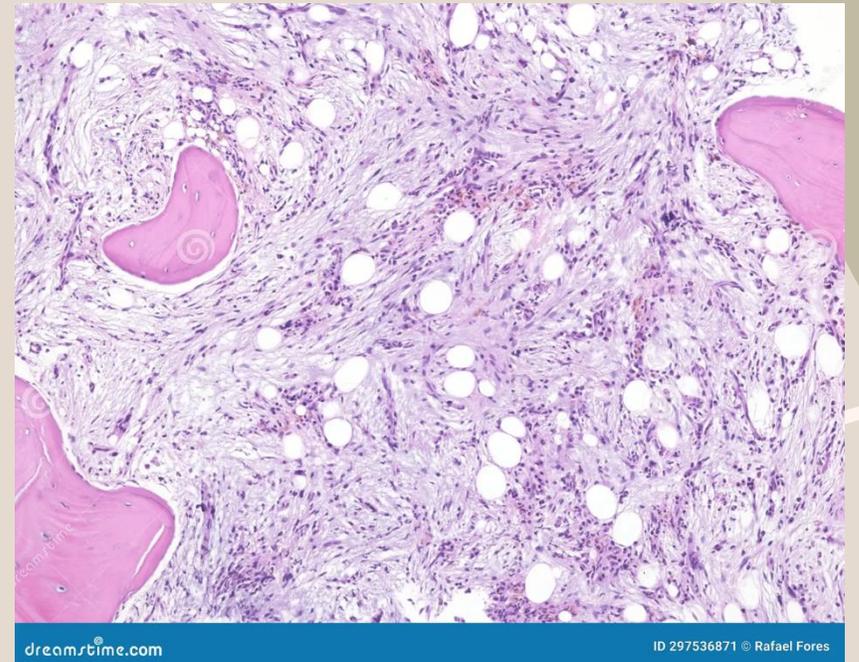
Essential Thrombocythemia (ET)

- Megakaryocyte proliferation with overproduction of platelets.
- Elevated platelet counts ($>600 \times 10^9/L$).
- ET is associated with activating point mutations in JAK2 (50%),
- Why some patients with JAK2 mutations present with PCV & others with ET : not understood.
- Bone marrow: cellularity is usually only mildly increased, but megakaryocytes are often markedly increased in number with abnormal large forms.
- Peripheral smears: usually reveal abnormally large platelets often accompanied by mild leukocytosis.
- A characteristic symptom : **Erythromelalgia**, a throbbing and burning of hands and feet caused by occlusion of small arterioles by platelet aggregates.



Primary myelofibrosis:

- The hallmark of primary myelofibrosis is the development of obliterative marrow fibrosis , and reduces bone marrow hematopoiesis:
- 1) Cytopenia.
- 2) Extensive extramedullary hematopoiesis.
- Histologically, the appearance is identical to the spent phase that occurs occasionally late in the course of other MPN.
- The characteristic marrow fibrosis is caused by the inappropriate release of fibrogenic factors from neoplastic megakaryocytes.



Thank
you

The text "Thank you" is written in a dark blue, elegant cursive script. The word "Thank" is on the top line and "you" is on the bottom line. The letters are highly stylized with large loops and flourishes. The word "Thank" features a yellow crescent moon on the left side of the 'T' and a red flower-like shape above the 'h'. The word "you" has a pink flower-like shape to its right. Various colorful accents, including small stars, hearts, and curved lines in shades of red, orange, teal, and yellow, are scattered around the text. The entire graphic is set against a white rectangular background.